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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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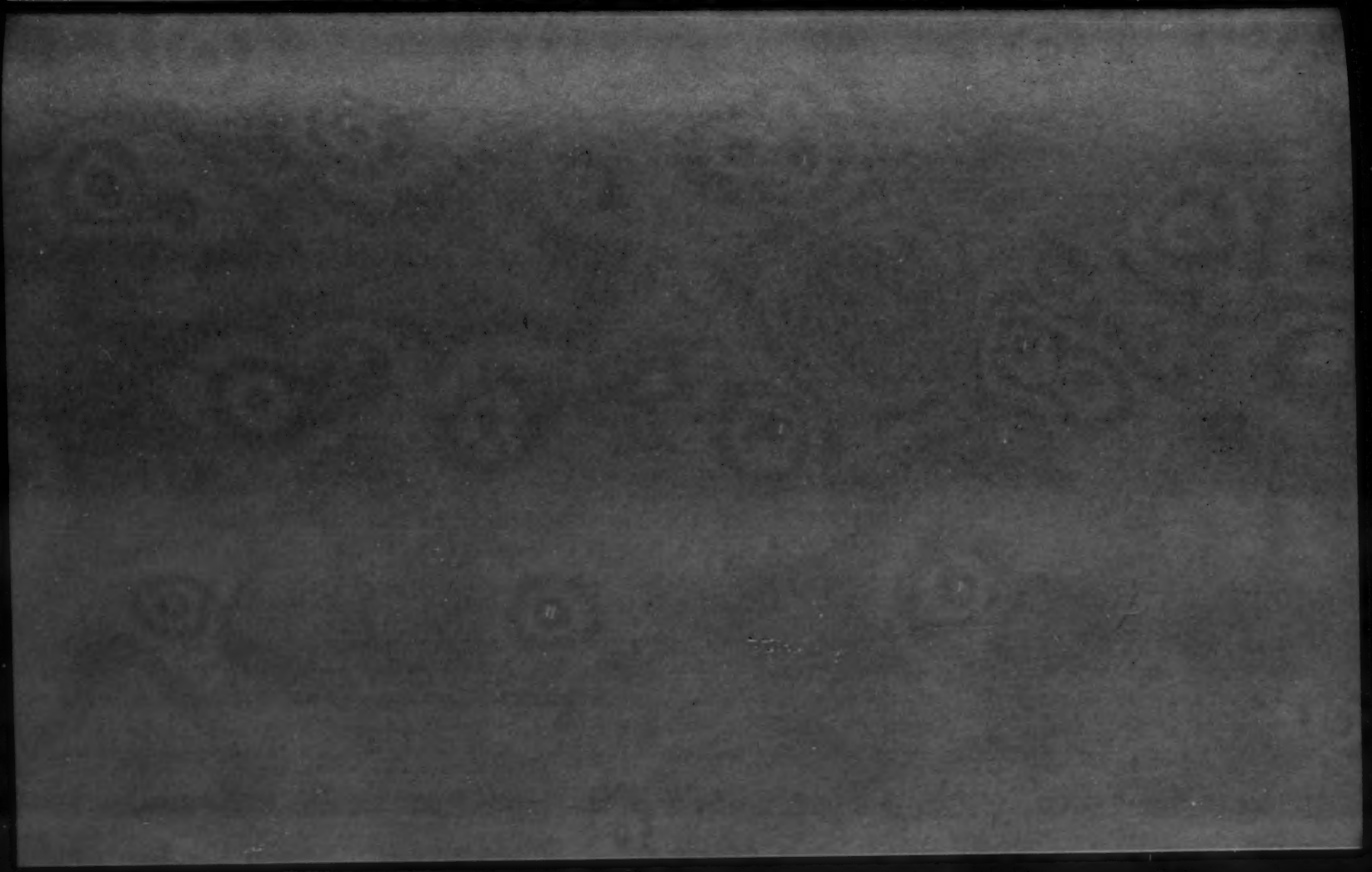

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CONTENTS

Epidemic Encephalitis 487
Ralph S. Muckenfuss

Progress in the Preoperative and Postoperative Care of Patients with Lesions of the Biliary Tract . . . 500
I. S. Ravdin

The Chemical and Physiological Properties, and Clinical Uses of the Corpus Luteum Hormone, Progesterone 508
Willard M. Allen

Chemical, Physiological and Clinical Aspects of the Androgens 519
John Eager Howard

Some Aspects of the Common Contagious Diseases . 532
Philip Moen Stimson

The Marriage of Medicine and Civil Government . . 548
Haven Emerson

Library Notes:
Recent Accessions 555

Proceedings of Academy Meetings 558

Deaths of Fellows 564

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BULLETIN OF
THE NEW YORK ACADEMY
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JULY 1941

EPIDEMIC ENCEPHALITIS*

RALPH S. MUCKENFUSS

Director of Bureau of Laboratories, New York City Department of Health

THE clinical picture of encephalitis was first brought to attention in 1917 when von Economo[1] described an outbreak of encephalitis which he called "lethargic encephalitis." During the following few years this disease was recognized as widespread over the world, and it shortly became apparent that the term "lethargic" was a misnomer. The accepted title was accordingly changed to "epidemic encephalitis."

For a time this term appeared satisfactory, but in 1924, 1927, and in several succeeding years a different form of encephalitis appeared in Japan. This type occurred characteristically in the late summer instead of predominating in the winter months, and had other features that classed it as a disease different from that described by von Economo. Kaneko and Aoki[2] designated this disease "type B" to distinguish it from the disease of von Economo, which was called "type A."

In the late summer of 1933 an epidemic of encephalitis similar in many respects to Japanese type B occurred in the city of St. Louis. This has been shown by investigations in the last few years to be of a different etiology from that of the Japanese disease.

* Read October 25, 1940 in The Graduate Fortnight of The New York Academy of Medicine.

An epidemic of encephalitis caused by the virus of equine encephalomyelitis of the eastern type occurred in Massachusetts in the summer of 1938, and in the same year human infections with the virus of the western type were reported.

Recently, encephalitis occurring in the spring and early summer in Russia and Siberia, and caused by a virus immunologically different from the viruses of St. Louis or Japanese encephalitis, has been described.

Thus it is evident that the term "epidemic encephalitis" must be broadened and that its use alone is no longer sufficient as a diagnosis. Retaining this general designation, the different forms of encephalitis, including von Economo's disease, Japanese encephalitis, St. Louis encephalitis, equine encephalomyelitis of the eastern type, equine encephalomyelitis of the western type and the recently described Russian encephalitis, must be differentiated. Australian X disease is a form of encephalomyelitis apparently occurring in epidemic form, but information concerning it is so limited that it will not be included in the present discussion.

Admittedly, there may still be cases of encephalitis of diverse and, as yet, unrecognized etiology. Future discoveries may necessitate still further differentiation.

Etiology

All of the diseases included under the generalization "epidemic encephalitis" are either caused, or presumed to be caused, by filterable viruses.

The *disease described by von Economo* was the first of the group to be recognized, and has been subjected to the most intensive investigations without success in establishing its etiology. Streptococci have been repeatedly suspected, but none of these claims has been sustained by further research. Several viruses have also been suspected, and the evidence is strongest for the herpes virus,[3] which is presumed to acquire neurotropic properties making it capable of causing encephalitis. Attractive as this hypothesis is, there are serious objections to it.

Herpes virus is rather widespread among human beings, and is usually isolated with little difficulty. Many strains can readily be shown to possess neurotropic properties for animals. If herpes virus is the cause of von Economo's disease, it is a little difficult to explain why its isolation from human cases of the disease has so rarely been accomplished.

It is worthwhile noting that this virus has been isolated from the central nervous system of persons suffering from other diseases of known etiology and in whom epidemic encephalitis had not been suspected. Unfortunately, the specific diagnosis of this disease is necessarily attended by some uncertainty, but the clinical histories of cases from which herpes virus has been isolated justify one in questioning whether all of them were actually cases of epidemic encephalitis. It has also been shown[4] that the occurrence of neutralizing antibodies against herpes virus in the blood of those suffering from the disease of von Economo is not significantly different from their presence in the general population.

These reports make it clear that herpes virus cannot be accepted as the established cause of the encephalitis of von Economo, and in my opinion the burden of evidence is against this virus having any part in its etiology. The cause of this disease must still be considered unknown.

St. Louis encephalitis is caused by a virus found in the central nervous system of fatal cases, and capable of causing a fatal infection in mice[5] and a non-fatal infection in *Macacus rhesus* monkeys[6] on intracerebral injection and in mice by intranasal instillation.[7] Attempts to infect other animals have usually failed, although the virus can persist for a short time in the brains of guinea pigs and rats,[8] and has been reported to have been passed serially in guinea pig brains[9] and in mouse testicles.[10] Histologically, the lesions produced in mice and in monkeys are analogous to those observed in humans. As described by McCordock,[11] "the essential pathologic process is an acute non-purulent inflammation of the central nervous system characterized by intense vascular congestion with petechial hemorrhages, cellular infiltration of both nervous tissue and meninges with various types of mononuclear cells, and evidences of toxic degeneration in the nerve cells." The virus of St. Louis encephalitis is neutralized by serum from persons who have recovered from the disease[5, 12] and is immunologically distinct from other viruses.[5, 12, 13]

Japanese type B encephalitis resembles St. Louis encephalitis and is caused by a virus infectious for mice[14, 15, 16] and monkeys.[14, 16] The infection in these animals is more severe than that caused by the St. Louis encephalitis virus, and the pathological findings are similar, though varying in intensity. The Japanese encephalitis virus is neutralized by convalescent serum[16, 17] and is immunologically different from the St. Louis

encephalitis virus[17, 13] and other viruses.[15] However, there is some evidence that the Japanese virus may be somewhat related to the St. Louis virus. Kuttner and T'ung[18] described two cases of encephalitis contracted by Europeans in China. The serum of one of these protected against both the Japanese and St. Louis encephalitis viruses and the serum of the other protected against the Japanese virus, but was not tested against the St. Louis virus. Webster[13] later tested these sera and found they both protected against the Japanese as well as the St. Louis virus. Several Japanese investigators[17, 19] have found that serum of rabbits immunized against the Japanese virus neutralized not only Japanese virus but also the St. Louis virus.

Equine encephalomyelitis occurs in two forms, the eastern type occurring east of the Appalachian mountains, and the western type occurring west of this mountain range. The two types are immunologically different.[20] A number of animals and birds are susceptible, and some of these have been found naturally infected. These facts may be of considerable epidemiological importance and will be discussed in greater detail later.

Russian encephalitis has recently been described[21, 22, 23] as being caused by a virus to which mice and monkeys are susceptible. This virus appears to be immunologically related to the virus of Japanese type B encephalitis, although the two are distinguishable by cross neutralization tests.

Epidemiology

von Economo Encephalitis. Numerous epidemics of von Economo's disease occurred throughout the world from 1920 to 1926, and since that time the incidence has been gradually diminishing. It is reasonable at this time to consider it endemic rather than epidemic. During the epidemic periods the incidence was highest during the winter months; during recent years this tendency to seasonal distribution has been less marked.

With knowledge lacking concerning the etiology, there can be little certainty concerning the mode of transmission or factors directly affecting the spread of this disease. The situation may best be summarized by quoting MacNalty:[24] the "epidemiological concept of encephalitis is therefore similar to that of various epidemic diseases of the central nervous system; thus, while associated groups of cases or definite epidemics

sometimes come to light, the ordinary train of evidence is that only here and there does the widespread infecting agent find an individual who reacts with unmistakable illness manifested by a characteristic syndrome. Alternatively, the agent may infect the individual with such a massive dose, or in such a special manner that the characteristic disease is produced. In other words, for every definite and characteristic case of encephalitis lethargica there is a large and indeterminate number of people who receive and carry the infection without themselves suffering noticeably or at all."

St. Louis Encephalitis. Though it was first recognized as a new etiologic entity during the outbreak in St. Louis, the disease resembled an outbreak of encephalitis in Paris, Illinois in 1932. The form of encephalitis in St. Louis may also have been present in New York City in 1933. It was definitely present in Kansas City in 1933, and a virus identical with that isolated in St. Louis was recovered there.[5] Sera from five convalescents in Paris, Illinois, in 1932, from two convalescents in New York City in 1933, and from four convalescents in Kansas City in 1933, were shown by Webster and Fite[12] to neutralize the virus of St. Louis encephalitis.

In the late summer and early fall of 1937 another outbreak of encephalitis similar to the one in 1933 occurred in St. Louis. This time a virus identical with that isolated in 1933 was recovered.[25] This was neutralized by serum of convalescents in 1933, and the 1933 virus was neutralized by serum of patients recovering from the disease in 1937.

Epidemics of St. Louis encephalitis have occurred characteristically in the late summer and early autumn. The fatality has averaged between 20 and 30 per cent and both the incidence and fatality have been higher in older age groups.

The etiological virus has been demonstrated only in the central nervous system of fatal cases. Failure to detect it in nasal washings or blood[6] may be due to its complete absence, to its presence for only a short time, or to the inadequacy of technical methods employed. The manner of spread of St. Louis encephalitis is consistent with that for a disease transmitted by droplet infection and by carriers. That mice can be infected by dropping the virus in the nose supports this possibility. Although the virus has never been recovered from nasal washings, there is indirect evidence that it may be present. Sulkin, Harford and Bronfenbrenner[26] dropped nasal washings from cases of St. Louis encephalitis

into the noses of mice and, although none of them developed encephalitis, active immunity in a high percentage of the mice was evident on subsequent intracerebral inoculation of the virus.

Whether a similar process of subclinical infection resulting in immunity occurs in man has not been definitely determined. But many investigators[27, 28] have reported the presence of neutralizing antibodies in presumably normal individuals—those who have no history of exposure to the virus. That such antibodies actually protect the individual against clinical infection is not known.

Biting insects were suspected as possible vectors, although the failure to demonstrate the virus in the blood stream makes it difficult to see how they could become infected. Experiments[11] designed to show transmission in this manner have uniformly failed, although Webster, Clow and Bauer[29] proved that *Anopheles quadrimaculatus* mosquitoes could become infected and would remain so throughout their entire lives. Mice rarely develop encephalitis if inoculated in any manner other than intracerebrally or intranasally. If mosquitoes are an important factor in the spread of St. Louis encephalitis, it is necessary to assume that infection through the skin by relatively small doses can be accomplished more readily in man than in experimental animals.

The situation concerning the transmission of St. Louis encephalitis was summarized by Leake[11] as follows: "In view of the trend of the insect experiments, the diffuse fashion in which poliomyelitis, except in the most intense epidemics, spreads through a community without apparent contact between cases, and in view of the radial spread of this epidemic of encephalitis by communities, but not by individual cases, it appears likely that human contact, chiefly through unrecognized carriers, is the method of infection here, but that susceptibility, in which age is an important factor, determines who will contract the disease in an infected community."

Contrary to Leake and his co-workers who could find no concentration of cases of encephalitis in any one district during the 1933 epidemic of encephalitis, Casey and Broun[30] reported that in 1933 and 1937 the cases of encephalitis in St. Louis were concentrated in the vicinity of small streams in areas characterized by the presence of weeds, refuse dumps, open sewage, and ponds. These are conditions that could favor the breeding and survival of mosquitoes.

Japanese Type B Encephalitis. Epidemiologically, Japanese type B

encephalitis is similar to St. Louis encephalitis, except that the fatality is higher, being over 50 per cent. The virus causes a more severe infection which is fatal in monkeys[13, 16, 17] and it is also capable of infecting young sheep.[13] It is uniformly present in the blood stream of mice in the early stages of infection, as demonstrated by Webster.[13] Furthermore, intraperitoneal or subcutaneous injection of the virus more frequently leads to infection in mice[17] than does similar inoculation of mice with St. Louis encephalitis virus. There are several reports[14, 15] of isolation of the virus from the spinal fluid of patients; this has not been reported in St. Louis encephalitis.

Mitamura and his co-workers[31] are of the opinion that mosquitoes play a part in the spread of the disease. In 1933 they concluded that the outbreaks of Japanese summer encephalitis could be explained only on the assumption that the disease was transmitted by mosquitoes. In 1937, using three species of mosquitoes, it was found that virus ingested by mosquitoes decreased in amount for a period and then increased until it reached practically the same concentration as that originally present. This took place in 10 days with *Culex pipiens var. pallens* and in from 15 to 20 days with *Aedes togoi.* Mosquitoes that had fed on human patients were also shown to be infective for mice.

Inada[32] is of the opinion that Mitamura's results show clearly that mosquitoes are the true reservoirs of the virus and that they may transmit the disease to laboratory animals by biting. However, the objection is raised that the number of cases in the towns affected is not in proportion to the distribution of the mosquitoes.

Equine Encephalomyelitis. There are at least five immunologically different forms of encephalomyelitis affecting horses.[33] Only the two forms occurring in the United States, the eastern and the western types, however, have been proved to infect man, and this discussion is accordingly limited to these two. Although there are differences, the similarities from an epidemiological standpoint are so great that both may be considered jointly.

The virus of equine encephalomyelitis is capable of infecting a number of animals[34] and birds.[34, 35, 36, 37] For a short time during the early stages of the disease the virus is present in the circulating blood.[38] Experimentally, transmission is possible by mosquitoes[33, 39] and by ticks.[40]

In 1930, Meyer, Haring and Howitt[41] demonstrated that an epidemic of encephalitis in horses in the San Joaquin valley was caused by a filter-

able virus, and that monkeys, rabbits, guinea pigs, rats and mice were susceptible, and that the guinea pig was the experimental animal of choice. Subsequently, in 1933, Ten Broeck and Merrill[20] isolated the eastern type of virus. In 1932 Meyer[42] suggested that the unusual form of encephalitis contracted by three men working with infected horses might be due to the same virus. In 1938 an epidemic of encephalitis occurred in Massachusetts, and Fothergill and his associates[43] and Webster and Wright[44] isolated the virus of the eastern type. In the same year Howitt[45] isolated the virus of the western type from a fatal infection in California. A proven case of human infection also occurred in Minnesota.[46]

In considering the epidemiology of equine encephalomyelitis, it should be remembered that it was first recognized in horses, and that many epidemics have occurred in this species, while in man sporadic cases have been recognized and only one small epidemic, that occurring in Massachusetts in 1938. The disease must therefore be primarily a disease of lower animals, capable of infecting man.

It is most natural to think of equine encephalomyelitis as a disease of horses, which suggests the horse as the reservoir of the disease. This is probably not the case. As pointed out by Ten Broeck, Hurst and Traub[38] the burden of evidence is against transmission of the disease by contact and in favor of some insect vector because of its prevalence in the late summer and fall, particularly in the salt marshes. However, the presence of the virus in the blood of horses for a relatively short time and the simultaneous occurrence of epidemics in widely separated areas are evidence against the horse as the reservoir. Based on this information, these authors, in 1935, suggested that birds should be considered as possible hosts, although at the time there was no direct evidence for this hypothesis.

In 1938, Tyzzer, Sellards and Bennett[36] recovered virus of the eastern type from an epidemic in ring-necked pheasants, and this observation was repeated by Van Roekel and Clarke.[37] Fothergill and Dingle[35] isolated virus from a pigeon. Moreover, a large number of birds and domestic fowls[34, 47] have proven susceptible to laboratory infection. Ten Broeck[47] in 1939, showed that the virus is present in the blood of some fowls in higher concentration and for a longer time than in the horse.

Mosquitoes have received the most attention in searching for a vector, and eight species have been shown capable of transmitting the dis-

ease under laboratory conditions.[33, 39]

These observations make it possible to explain the epidemiology of equine encephalomyelitis, but it must be stressed that there are still many gaps in the evidence and that other possibilities must be considered. For instance, Syverton and Berry[40, 48] have shown that the gopher or ground squirrel is susceptible, that the tick is capable of transmitting the disease, and that the offspring of infected ticks are themselves infected.

Russian Encephalitis. The form of encephalitis occurring in the spring and summer in Russia and reported from the laboratories of Smorodintseff[21, 22, 23] by a group of collaborators seems to have the following characteristics:

1. It is endemic in the forest regions and is limited to people working in the forests.
2. It seems to remain in the endemic areas without spreading from them.
3. It does not show the higher mortality in older age groups characteristic of the St. Louis and Japanese encephalitis.
4. Rodents in endemic areas are infected. Some of them show no apparent illness, and the virus appears in the blood stream.
5. Ticks in endemic areas are infected and are capable of transmitting the disease.
6. The virus is serologically related to, but distinguishable from, the virus of Japanese encephalitis.

The Russian observers believe that the disease is one of rodents and that man is only incidentally infected.

Symptomatology and Diagnosis

The symptomatology and diagnosis of encephalitis are considered at this point rather than earlier, because epidemiological considerations must enter into a differential diagnosis.

von Economo's disease has an acute stage lasting a few days characterized by slight fever, dizziness, diplopia, ocular paralyses, and sometimes headache, some stiffness of the neck, and a mild pleocytosis in the spinal fluid, usually about fifty cells. The symptoms are variable and in about half of the cases are so mild as to pass unnoticed or not to suggest encephalitis. It may be months or even years later that the sequelae (or more correctly the chronic stage) make the diagnosis evident.

The course of the disease, although variable in the extreme, classes

patients logically into the following groupings, according to Josephine Neal: 1. those that make a complete recovery; 2. those in whom the disease is progressive; 3. those in whom there is progression of the disease after some delay; and 4. those in whom the disease progresses with remissions.

In the chronic stage, contractures, spasticity, mental deterioration, and Parkinson's syndrome are particularly characteristic.

The other types of encephalitis discussed are so similar in their clinical manifestations in the acute stage that they may be considered together. Although there may be a short period of invasion, the onset is usually sudden, with fever, headache, occasionally vomiting, stiff neck, and pleocytosis in the spinal fluid, usually in the neighborhood of 200 to 300 cells. Mononuclear cells predominate, except apparently in equine encephalomyelitis where neutrophiles[43] seem to be preponderant.

Differentiation may be made on the following points:

1. Only St. Louis encephalitis and equine encephalomyelitis have been recognized in the United States.
2. The highest incidence of these diseases is in the late summer and fall.
3. Specific neutralizing antibodies may be demonstrated after recovery.
4. Virus may be isolated from the central nervous system of fatal cases and may be identified.
5. Serious sequelae are rather rare after St. Louis encephalitis, but common after equine encephalomyelitis.
6. Older people are particularly susceptible to St. Louis encephalitis; this is not true of equine encephalomyelitis.

It should be emphasized that on clinical grounds alone a positive differentiation of the different forms of epidemic encephalitis is not possible. It is only with the aid of the laboratory that this may be accomplished.

There are other forms of encephalitis, for example, postinfectious encephalitis, and other infections of the central nervous system, which may confuse the diagnosis. These must be differentiated in making the diagnosis, but are not considered in this paper.

Treatment

Treatment of all the infections included under the generalization "epidemic encephalitis" is symptomatic. Lumbar puncture frequently

relieves headache, and sedation may be necessary. Relief of the distressing manifestations of the chronic stage of von Economo's disease has been most successful following administration of belladonna derivatives, particularly in recent years, Bulgarian belladonna, sometimes called bella bulgara. Many other therapeutic measures have been tried with varying opinions concerning their value.

Prophylaxis

Prophylaxis, in the absence of specific immunizing agents, must depend on general measures. It seems reasonable to isolate patients during the acute stages, to restrict visiting, to have attendants wear masks, to disinfect bedding, discharges, and dishes, and to screen rooms. Screening seems particularly justifiable in areas where equine encephalomyelitis is present in animals. Vaccination of horses against equine encephalomyelitis with formalinized chick embryo vaccine appears to be of value; in man this vaccine has been used with apparent success in laboratory workers intimately exposed to the virus. It is too early to state whether the use of the vaccine under field conditions is advisable.

Summary

Epidemic encephalitis must now be considered a general term embracing a number of etiologically distinct infections of the central nervous system which must be identified individually for diagnosis. Since all are so similar epidemiologically, clinically and pathologically, their differentiation is possible only with the aid of the laboratory where etiologic studies or neutralization tests can be carried out to establish the diagnosis. The manner of spread of these diseases is, for the most part, unknown, but some appear to have a reservoir in lower animals and to attack man through the bites of insects.

REFERENCES

1. von Economo, C. Encephalitis lethargica, *Wien. klin. Wchnschr.*, 1917, *30:* 581.
2. Kaneko, R. and Aoki, Y. Ueber die Encephalitis epidemica in Japan, *Ergebn. d. inn. Med. u. Kinderh.*, 1928, *34:* 342.
3. *Epidemic encephalitis;* First, Second and Third Reports by the Matheson Commission. New York, Columbia University Press, 1929, 1932 and 1939.
4. Andrewes, C. H. and Carmichael, E. A. Note on the presence of antibodies to herpes virus in post-encephalitic and other human sera, *Lancet,* 1930, *1:*857.
5. Webster, L. T. and Fite, G. L. A virus encountered in the study of material from cases of encephalitis in the St.

Louis and Kansas City epidemics of 1933, *Science*, 1933, *78:*463.

6. Muckenfuss, R. S., Armstrong, C. and McCordock, H. A. Encephalitis; studies on experimental transmission, *Pub. Health Rep.*, 1933, *48:*1341.
7. Webster, L. T. and Fite, G. L. Experimental studies on encephalitis; the specific virus character of the infectious agent from cases of St. Louis and Kansas City encephalitis, 1933, *J. Exper. Med.*, 1935, *61:*411.
8. Smith, M. G. Survival of the virus of St. Louis encephalitis in rats and guinea pigs, *J. Infect. Dis.*, 1939, *64:*307.
9. Sulkin, S. E., Harford, C. G. and Bronfenbrenner, J. Attempts to infect guinea pigs with the virus of St. Louis encephalitis, *Proc. Soc. Exper. Biol. & Med.*, 1939, *41:*329.
10. Lennette, E. H. and Smith, M. G. The propagation of St. Louis encephalitis virus in mouse testicle, *Proc. Soc. Exper. Biol. & Med.*, 1939, *41:*193.
11. U. S. Public Health Service. Report on the St. Louis outbreak of encephalitis, *Pub. Health Bull.*, 1935, No. *214*.
12. Webster, L. T. and Fite, G. L. Contribution to the etiology of encephalitis; differentiation of encephalitis by protection tests, *Proc. Soc. Exper. Biol. & Med.*, 1933-34, *31:*344.
13. Webster, L. T. Japanese B encephalitis virus; its differentiation from the St. Louis encephalitis virus and its relationship to louping ill virus, *J. Exper. Med.*, 1938, *67:*609.
14. Kaneko, R. *et al.* Tierexperimentelles zur Überimpfung von Encephalitis epidemica Typus B, *Klin. Wchnschr.*, 1936, *15:*674.
15. Kasahara, S. *et al.* Experimental studies on epidemic encephalitis; transmission test of the Japanese encephalitis in 1935 and some characteristics of the infectious agent, *Kitasato Arch. Exper. Med.*, 1936, *13:*48.
16. Kawamura, R. *et al.* Epidemic encephalitis in Japan; the causative agent compared with that in the St. Louis epidemic, *Arch. Path.*, 1936, *22:*510.
17. Kudo, M., Uraguchi, K., Matsuda, S. and Hashimoto, H. Experimental studies on the encephalitis virus of the 1935 epidemic in Tokyo, with special reference to its serological difference from the virus of St. Louis encephalitis, *J. Immunol.*, 1937, *32:*129.
18. Kuttner, A. C. and T'ung, T. Encephalitis in North China; results obtained with neutralization tests, *J. Clin. Investigation*, 1936, *15:*525.
19. Kasahara, S., Yamada, R. and Hamano, R. Experimental studies on epidemic encephalitis; immunological comparison of viruses of the Japanese (B type) and the American (St. Louis) types, *Kitasato Arch. Exper. Med.*, 1937, *14:*229.
20. Ten Broeck, C. and Merrill, M. H. A serological difference between eastern and western equine encephalomyelitis virus, *Proc. Soc. Exper. Biol. & Med.*, 1933-34, *31:*217.
21. Chumakov, M. P. and Seitlenck, N. A. Tick-borne human encephalitis in the European part of USSR and Siberia, *Science*, 1940, *92:*263.
22. Silber, A. L. Vernal (verno-aestival) endemic tick-borne encephalitis, *Arch. Biol. Sc., J. All Union Inst. Exper. Med.*, 1939, *56, pt. 2:*27.
23. Smorodintseff, A. A., Neustroew, V. D. and Drovishevskaya, A. L. On the susceptibility of rodents to artificial infection with the spring-summer and summer (Japanese) encephalitis, *Arch. Biol. Sc., J. All Union Inst. Exper. Med.*, 1939, *56, pt. 2:*146.
24. MacNalty, A. The epidemiology of encephalitis lethargica, *Proc. Roy. Soc. Med.*, 1937-38, *31:*1.
25. Greutter, J., Broun, G. O., Muether, R. O. and Casey, A. E. Further studies on the virus of the 1937 outbreak of encephalitis in St. Louis, *Proc. Soc. Exper. Biol. & Med.*, 1937-38, *37:*284.
26. Sulkin, S. E., Harford, C. G. and Bronfenbrenner, J. Immunization of mice by intranasal instillation of nasopharyngeal washings from cases of St. Louis encephalitis, *Proc. Soc. Exper. Biol. & Med.*, 1939, *41:*327.
27. Muckenfuss, R. S., Smadel, J. E. and Moore, E. The neutralization of encephalitis virus (St. Louis, 1933) by se-

rum, *J. Clin. Investigation*, 1938, *17:*53.

28. Wooley, J. G. and Armstrong, C. The distribution of immunity against encephalitis virus of the St. Louis type in the United States as determined by the serum-protection test in white mice, *Pub. Health Rep.*, 1934, *49:*1495.
29. Webster, L. T., Clow, A. D. and Bauer, J. H. Experimental studies on encephalitis; survival of encephalitis virus (St. Louis type) in Anopheles quadrimaculatus, *J. Exper. Med.*, 1935, *61:*479.
30. Casey, A. E. and Broun, G. O. Epidemiology of Saint Louis encephalitis, *Science*, 1938, *88:*450.
31. Mitamura, T. *et al.* Ueber den Infektionsmodus der epidemischen Enzephalitis. Experimentelle Untersuchungen über ihre Ansteckung durch Mücken, *Tr. Soc. path. Jap.*, 1937, *27:*573.
32. Inada, R. Compte rendu des recherches sur l'encéphalite epidémique au Japan, *Bull. Office internat. d'hyg. pub.*, 1937, *29:*1389.
33. Gordon, J. E. Infection of man with virus of equine encephalomyelitis, *Am. J. M. Sc.*, 1939, *198:*437.
34. Giltner, L. T. and Shahan, M. S. Transmission of infectious equine encephalomyelitis in mammals and birds, *Science*, 1933, *78:*63.
35. Fothergill, L. D. and Dingle, J. H. A fatal disease of pigeons caused by the virus of the eastern variety of equine encephalomyelitis, *Science*, 1938, *88:*549.
36. Tyzzer, E. E., Sellards, A. W. and Bennett, B. L. The occurrence in nature of "equine encephalomyelitis" in the ring-necked pheasant, *Science*, 1938, *88:*505.
37. Van Roekel, H. and Clarke, M. K. Equine encephalomyelitis virus (eastern type) isolated from ring-necked pheasant, *J. Am. Vet. M. A.*, 1939, *94:*466.
38. Ten Broeck, C., Hurst, E. W. and Traub, E. Epidemiology of equine encephalomyelitis in the eastern United States, *J. Exper. Med.*, 1935, *62:*677.
39. Kelser, R. A. Transmission of the virus of equine encephalomyelitis by Aedes taeniorhynchus, *J. Am. Vet. M. A.*, 1938, *92:*195.
40. Syverton, J. T. and Berry, G. P. The tick as a vector for the virus disease, equine encephalomyelitis, *J. Bact.*, 1937, *33:*60.
41. Meyer, K. F., Haring, C. M. and Howitt, B. The etiology of epizootic encephalomyelitis of horses in the San Joaquin Valley, 1930, *Science*, 1931, *74:*227.
42. Meyer, K. F. A summary of recent studies on equine encephalomyelitis, *Ann. Int. Med.*, 1932, *6:*645.
43. Fothergill, L. D. *et al.* Human encephalitis caused by the virus of the eastern variety of equine encephalomyelitis, *New England J. Med.*, 1938, *219:*411.
44. Webster, L. T. and Wright, F. H. Recovery of eastern equine encephalomyelitis virus from brain tissue of human cases of encephalitis in Massachusetts, *Science*, 1938, *88:*305.
45. Howitt, B. Recovery of the virus of equine encephalomyelitis from the brain of a child, *Science*, 1938, *88:*455.
46. Eklund, C. M. and Blumstein, A. The relation of human encephalitis to encephalomyelitis in horses, *J.A.M.A.*, 1938, *111:*1734.
47. Ten Broeck, C. Transmission of equine encephalomyelitis, *Proc. Third Internat. Cong. Microbiology*, 1939: 300.
48. Syverton, J. T. and Berry, G. P. Susceptibility of the "gopher," *Citellus Richardsonii* (Sabine) to equine encephalomyelitis, *Proc. Soc. Exper. Biol. & Med.*, 1936, *34:*822.

PROGRESS IN THE PREOPERATIVE AND POSTOPERATIVE CARE OF PATIENTS WITH LESIONS OF THE BILIARY TRACT*

I. S. RAVDIN

George Lieb Harrison Professor of Surgery
University of Pennsylvania School of Medicine

I SHALL confine my remarks this evening to certain aspects of the pathologic physiology of the liver, with which we have had some experience during the past few years.

Because of the intimate relationship of cholecystitis and hepatitis, there is frequently some hepatitis present before the effect of ductal occlusion from stone still further damages the hepatic cells. That extensive hepatitis may coexist with simple gallstone disease is not so generally accepted but it is nevertheless true. The occlusion of the common bile duct by a stone is further complicated by the fact that in most instances the gall bladder is at that time moderately or severely damaged. Under such circumstances the failure of the gall bladder to concentrate the trapped bile for a period leads to a rapid increase in the extra- and intrahepatic bile pressure so that hepatic secretory suppression occurs at an earlier period after obstruction.

The opportune time, therefore, to operate on a patient with gall stones is early when the stones are still present in the gall bladder and when the patient is suffering from the classical dyspepsia, or colic, or both, of simple calculous disease. It is, moreover, of importance to remove any calculi from the common duct at the primary operation. The time honored concept that a previous history of jaundice is the indication for common duct exploration has too frequently resulted in the primary or secondary operation being done following extensive liver injury or even during a period of intense obstructive jaundice, when the risk of operation is greatly increased.

In no field of surgery has the physiologic approach to the problems of preoperative and postoperative care had a greater influence, or saved

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From the Harrison Department of Surgical Research, University of Pennsylvania School of Medicine and the Surgical Clinic of the Hospital of the University of Pennsylvania.

more lives, than in the treatment of advanced biliary tract disease. The high mortality in the past can be ascribed neither to less technical skill nor to poorer surgical judgment, but rather to the lack of information concerning the pathologic physiology of the processes involved and the manner by which they can best be controlled prior and subsequent to operation. The special methods of preparation and after care have been based in large part on experimental studies.

The preoperative preparation of the patient should be directed toward correcting, as far as possible, any existing collateral disease, preventing postoperative hemorrhage, and altering the composition of the hepatic cells so as to prevent further liver injury and to allow for repair. I shall not discuss coexisting cardiac or pancreatic disease except to state that neither of these conditions should be considered as an insurmountable barrier to operation. If the patient is properly prepared for operation, with the help of a competent internist, the added risk of either of these conditions is not great.

Angina pectoris may be mimicked in every way by gall-stone disease. We have had a number of examples of this when stones have been present in the common duct, even though jaundice has never been present. Surely operations on or injections of the sympathetic nervous system should not be undertaken without first subjecting the patient to adequate surgery for the gall-stone disease if this is present and the effort syndrome of angina pectoris is absent.

It is generally believed that hepatic disease is unassociated with renal dysfunction. While in general this may be true, there occurs in a number of patients with obstructive jaundice a serious impairment of the functional activity of the renal parenchyma. It is in this group of patients that a low serum calcium may be encountered, which is nearly always associated with a serum protein deficiency or with hyperphosphatemia. These are even more apt to be present if the patient had preexisting renal disease. A preoperative high blood non-protein nitrogen in these patients is not always of serious significance for subsequent to surgical therapy the evidences of renal injury may rapidly subside. In the absence of a history of previous renal injury the high blood nonprotein nitrogen concentration need not alarm one unnecessarily, unless the entire clinical picture, at the same time, warrants alarm.

The evidence of renal impairment should in the main be considered as an additional load which has been added to that which the patient

is already carrying. It must be taken into account in preparing the patient for operation, and in determining the anesthetic to be used for operation. Above all, it must be considered in the administration of fluids, especially large amounts of sodium chloride, which may so tax a renal system, which is near the breaking point, as to result in renal insufficiency.

The advent of ductal occlusion causes serious disturbances in the physiology of the liver. The cells continue to secrete bile until the pressure in the bile ducts equals the secretory pressure of the liver. The presence of previously impaired gall-bladder function results in a shorter period of time between occlusion and icterus. When the intrahepatic bile pressure reaches from 280 to 330 millimeters, pigment does not pass through the hepatic cells and deep icterus results. Any further secretion is from the cells lining the ducts and results in the formation of what is commonly called "white bile."

The increase in ductal pressure which occurs following occlusion causes a retardation of the portal blood flow and thus there may develop local hepatic anoxia in the face of some evidence of an increased oxygen consumption in the liver during obstructive jaundice. Since the liver cells are extremely sensitive to oxygen want, further hepatic injury ensues. Thus the primary hepatitis, if this was present, is accentuated by the increased pressure in the intrahepatic bile ducts, and by the secondary anoxia. The injured liver cell is less capable of holding, and of storing glycogen. It rapidly loses its stores of mobile protein and may not normally synthesize protein. It is incapable of normally metabolizing the fat which comes to it and there is apt to occur fatty infiltration. The latter process is more apt to be excessive when there is considerable fat in the subcutaneous tissues.

While it was previously believed that the liver glycogen protected the liver against injury during anesthesia, information which we have obtained leads us to state that it is the liver fat which conditions liver necrosis subsequent to the use of volatile anesthetics. The increase of the liver glycogen is valuable, therefore, only if by increasing the liver glycogen, liver fat is reduced, that is, if the reciprocal relationship between glycogen and fat described by Rosenfeld is fulfilled. It is also probable that an adequate amount of hepatic glycogen will, to a degree, protect the protein stores of the liver. Observations which we have made on the dog and on a series of patients with serious hepatic injury, who

were prepared for operation by a high carbohydrate diet and the intravenous administration of glucose for from eight to fourteen days prior to operation, force me to state that often there remained in the liver concentrations of fat which might have resulted in further serious liver injury, had a volatile anesthetic been used.

The plan which we are now using is as follows: The patients, if they can be made to eat, are given a diet which consists of 75 to 80 per cent of their calories as carbohydrate to which is added protein in an amount of 20 per cent of the total calories. The diet is given in small amounts but at frequent intervals, so that the total caloric intake is, if possible, about 3,000 calories per day. The protein is added because it assists the carbohydrate in reducing the hepatic lipid concentration; it aids in the prevention of injury by certain hepatotoxic agents; and, furthermore, unless sufficient stores of protein are present, tissue regeneration cannot take place. In addition to the carbohydrate-protein meal we give these patients approximately 10 milligrams of crystalline vitamin B_1 and a varying amount of desiccated bile daily. With such a method we have increased the liver glycogen concentration in the presence of complete ductal occlusion in the experimental animal to as much as 12 per cent, a concentration which previously we had thought unattainable, and we have simultaneously reduced the liver fat from levels as high as 50 per cent to a normal level over a period of one week.

The use of substances containing vitamin K_1 or K_2 or of the synthetic quinone derivatives having a K-like action has made postoperative hemorrhage an exceedingly rare complication. In doses of 2 milligrams, three times a day, 2-methyl-1,4-naphthoquinone is effectual in restoring a normal prothrombin time in the great majority of patients within 72 hours. It is even more potent than the naturally occurring vitamin.

The hemorrhagic tendency of the jaundiced patient is due to a prothrombin deficiency conditioned by the absence of bile salt from the intestinal tract. When the vitamin K substrates and synthetic substitutes are used bile salts should be used with them. The soluble synthetic K substitutes can be used intravenously.

All severely jaundiced patients who have not responded to K therapy are placed on a forced diet and are transfused prior to operation. Our practice has been to use small amounts, 250 to 300 cubic centimeters of blood, for two or three days before the contemplated exploration. This serves several purposes. It improves the quantity and the

quality of the blood; it provides serum protein which may be deficient; and it improves the oxygen-carrying capacity of the blood.

We have come to believe that early operation, once occlusion has occurred, is not always to be desired. It has been our policy to withhold operation when the bilirubin concentration in the serum is increasing or decreasing. If it is increasing or decreasing, we wait until the concentration reaches a plateau. During this period the patient is being prepared for operation. Except where suppuration is suspected, the operation is safer when hepatic function has stabilized itself against a high or low serum bile pigment concentration and an adequate program of therapy has been carried out.

In the light of available evidence we believe that the anesthetic of choice is spinal anesthesia. We have good evidence that ether may cause serious liver injury in the presence of the conditions often existing during ductal occlusion. Nitrous oxide and oxygen, when pushed to the point of even semi-satisfactory relaxation, causes an anoxia which results in further liver injury. Cyclopropane may be satisfactory but there is as yet insufficient evidence as to its effect on the hepatic parenchyma, especially in the presence of high concentrations of hepatic lipid, to warrant its widespread adoption.

Spinal anesthesia, in which marked depression of the blood pressure is prevented by the preanesthetic administration of adequate doses of ephedrine, has proven so satisfactory in our hands that until a better method is demonstrated we shall continue to use it. Carefully administered, it is, we believe, the safest anesthetic in these bad risk patients.

We believe that the subcostal incision affords better exposure of the biliary passages, is associated with less postoperative pain, fewer pulmonary complications and a lower incidence of postoperative herniation than any other incision. Its full advantages are never appreciated until it is used.

I shall not discuss the various technical details necessary to complete the operation satisfactorily. In the presence of stone obstruction a thorough search is essential and the removal of a single stone is not sufficient reason for terminating the exploration. Not until the operator is satisfied that there are no stones in the right or left duct and a catheter can be freely passed into the duodenum is his responsibility for further exploration at an end.

As soon as the opening in the common duct is closed around the tube,

fluid is introduced through the open end of the tube and the tube is then clamped. When the patient is returned to his bed the free end of the tube is attached to a "decompression" apparatus and this is so arranged that the top level is kept at approximately 200 millimeters above the common duct. Over a period of days this is gradually lowered but it is never lowered to the point where large amounts of bile are permitted to drain externally.

The use of this principle serves several useful purposes. In the first place, it prevents an acute hepatic hyperemia subsequent to release of the ductal occlusion. After the sudden release of a complete ductal occlusion there is often observed an intense hyperemia of the liver tissue and the extravasation of large amounts of blood in the perivascular spaces. Although decompression occurs in part during the operation, the maintenance of an adequate pressure level thereafter is, we believe, of real help in preventing massive extravasation of blood into the liver tissue. Furthermore, it overcomes the defect of the older method of drainage into a bottle at the bedside in that large amounts of bile are not sucked into the container. This added advantage of permitting the bile to enter the intestine at an early period is obvious. The fluid and electrolyte balance is more easily maintained and the extrahepatic functions of the bile are reëstablished within a short time after operation. The effects of excessive external bile drainage were described some years ago by William Halsted who personally experienced them. The lassitude, weakness, anorexia, rapid pulse and even comatose state so frequently observed in such patients can in large measure be prevented by the use of the "decompression" principle. The additional advantage of the bile subserving a useful intestinal function I shall describe later.

No tube should be removed from the common duct before a cholangiogram has been made. Even the most experienced of surgeons will occasionally leave a stone behind. The time to know this is before the "T" tube is removed. It is then that the Pribram method may be used with some hope of success.

In the administration of fluid during this period one must be guided by the principles laid down by Wiley and Newburgh and their elaboration by Coller and Maddock. The control of the postoperative administration of intravenous fluids to these patients is not to be left to one of a group of constantly changing interns, nor can the quantity or type be determined routinely for all patients.

As soon as the stomach is retentive, food should be given by mouth. The diet which we have used in the postoperative period is again a carbohydrate-protein mixture, practically devoid of fat. With such a regime regeneration of liver cells may occur rapidly and normal function, if this can be restored, will make its appearance at an earlier period than when the patient is on a haphazard diet or on a regime which restricts food by mouth beyond the necessary period. It is not possible to furnish the energy requirements of the patient and increase the liver glycogen and protein storage by intravenous therapy. Protein wastage will be prevented, liver glycogen stores will be built up, liver fat displaced, and cell regeneration take place when the total food intake is more than sufficient to cover the energy requirements. Data which we plan soon to publish lend no support to Soskin's concept of a physiological basis for intravenous glucose in these patients.

The restoration of bile to the intestinal tract at an early period by the use of a "decompression" apparatus, if the lower end of the common duct is patent, has already been mentioned. The most important function of the bile is its intestinal function. The activation of lipases, the emulsification of fats and their transport across the intestinal membrane, and the aid in the absorption of accessory food substances, such as vitamins A and K, are but a few of the activities which bile plays in the small bowel.

For some time we replaced part of the bile drained to the exterior through a gastric tube, and still use this method when edema or inflammatory exudate prevent the entrance of bile directly into the duodenum.

With the decompression method bile flows directly into the duodenum. Convalescence is smoother, and we have had an absence of the asthenic states which were so often observed when excessive external biliary drainage occurred. The asthenia which Whipple called, for want of a better name, "pancreatic asthenia" has been rarely observed by us since we began the routine use of decompression nine years ago. It is, we believe, due to a disturbance of intestinal and hepatic physiology and is the result, in part, of an interference with the extrahepatic functions of the bile. Why it makes its appearance in some patients and not in others; and why it is often not observed after prolonged ductal occlusion prior to operation, I cannot explain.

I have discussed a few of the factors which must be considered in caring for these desperately ill patients before, during and after opera-

tion. In each of them there are present certain profound physiological disturbances, some of which are understood and others of which remain to be elucidated. The risk of operation will be reduced if attempts are made prior, during, and subsequent to operation to restore function to as nearly normal as is possible. Such a program has resulted on my service in the Hospital of the University of Pennsylvania in a very desirable reduction in the morbidity and mortality of operations on these seriously ill patients. Further improvement in our immediate and late results will come from a fuller understanding of the conditions imposed on the organism in the presence of acute and chronic hepatic injury and the mechanism by which these pathological states may be controlled or corrected prior to operation.

THE CHEMICAL AND PHYSIOLOGICAL PROPERTIES, AND CLINICAL USES OF THE CORPUS LUTEUM HORMONE, PROGESTERONE*

WILLARD M. ALLEN

Professor of Obstetrics and Gynecology,
Washington University School of Medicine, St. Louis

THE corpus luteum hormone, progesterone, owes its discovery to two events: First, a considerable amount of physiological experimentation indicated the production of a special hormone by the corpus luteum; second, after the preparation of active estrogenic extracts it was found that these preparations did not produce the effects characteristic of the corpus luteum.

The first actual experiments to establish the corpus luteum as an endocrine gland were made by Fraenkel[1] in 1903. He found that removal of the corpora lutea in the first few days of pregnancy prevented the continuation of pregnancy. Loeb[2] in 1907 made the next contribution by showing that the endometrium of the guinea pig is sensitized while under the influence of the corpus luteum so that simple, mechanical trauma at the time when the embryos would be implanting, results in the formation of a decidual tumor at the site of injury. This experiment showed that the endometrium requires the presence of the corpus luteum before it can respond normally to the presence of the embryo. A little later, in 1910, Bouin and Ancel[3] showed in the rabbit that the endometrium undergoes marked proliferative changes as the corpus luteum develops, and further, that removal of the corpora lutea prevents this proliferation. Here then was the first evidence that actually the embryos in Fraenkel's experiments arrived in a uterus which was not prepared by the action of the corpus luteum to receive them. Coincident with the growth of the corpora the endometrium proliferates rapidly, as we now know because of the action of progesterone, and the embryos survive. If the corpora are removed, this proliferation does not take place and growth of the embryo stops, as was shown by Corner[4] in 1928, as soon

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as it reaches the uterus. This proliferation is essential for the implantation of the embryo, and hence has been called progestational proliferation.

Alterations of the endometrium of similar significance are found in association with the growth of the newly formed corpus luteum in all species that have been investigated, and in the woman we now know that the premenstrual changes are due in part at least to the progesterone produced by the corpus luteum. Such alterations, no matter how dissimilar they may appear to be in different species, are essential for the safe implantation of the embryo.

The corpus luteum hormone, of course, has many properties other than those specifically pertaining to the uterus but they are presumably all related to the problem of preparing the body for pregnancy and the safe continuation of pregnancy.

None of the specific effects of the corpus luteum can be satisfactorily and completely produced by estrogens. Pregnancy cannot be maintained in a castrated rabbit with estrogen. The endometrium of the guinea pig cannot be sensitized by estrogens. Premenstrual changes cannot be produced in primates with estrogens. For these reasons, George Corner and I began our work on extracts of the corpus luteum.

To study the effect of a corpus luteum extract, it is necessary only to castrate the rabbit about eighteen hours after mating, and then to give the preparation to be tested for five days to see what effect it will have on the endometrium and on the embryos. If the extract contains no corpus luteum hormone, the endometrium shows no progestational proliferation and the embryos do not develop; if on the other hand the extract contains corpus luteum hormone, the uterus undergoes typical progestational changes and the embryos develop exactly as in normal pregnancy, even though the rabbit has been deprived of her own corpora lutea almost from the time of ovulation.

This method of testing the extracts enabled Corner and myself to prepare active crude extracts of the corpus luteum. These crude extracts produced progestational changes in the endometrium, maintained pregnancy to term in castrated rabbits and sensitized the guinea pig's endometrium so that deciduomata could be produced experimentally. In short, these crude extracts contained a hormone (or hormones) which did all the things that the corpus luteum was supposed to do, at least in so far as the rabbit and guinea pig are concerned. Because of its

obvious relation to pregnancy, it was named progestin, i.e., a substance necessary for pregnancy.

The active principle was independently isolated in 1934 by Butenandt;[5] Slotta, Ruschig and Fels;[6] Allen and Wintersteiner;[7] and Hartmann and Wettstein.[8] It was found to be a neutral compound, a di-ketone with the empirical formula $C_{21}H_{30}O_2$. This immediately suggested that it was closely related to pregnandiol, a dialcohol previously isolated by Marrian[9] in 1929 from the urine of pregnant women, with the formula $C_{21}H_{36}O_2$, the detailed structure of which had already been established by Butenandt.[10] The supposed relationship was proved soon by Butenandt by the preparation of progesterone from pregnandiol and from stigmasterol. It has since been prepared from cholesterol and sarsapogenin and possibly other sterols.

Progesterone is soluble in most organic solvents, and in vegetable oils, such as sesame oil, olive oil and peanut oil, but it is insoluble in water. It is ordinarily dissolved in a bland vegetable oil and is given by intramuscular injection. Despite its insolubility in water, absorption from the oily solutions is quite rapid. The effect is not prolonged and anyone who has had much experience with the use of progesterone in animals gives little credence to reported remarkable clinical results where small doses were given once weekly. For example, in certain experiments in rabbits the omitting of a single daily dose may be sufficient to disturb a pregnancy being maintained artificially by progesterone. In women, too, progesterone deprivation frequently is followed by menstrual bleeding within forty-eight hours. If one is attempting therapy with progesterone, injections should be given each day. In this respect it is quite different from the esters of estradiol and testosterone, the absorption of which extends over a period of several days.

The conditions for which progesterone may be used in women are probably rather few but before discussing them it may perhaps be profitable to mention some of the physiological effects in animals. The endometrium of the rabbit responds to progesterone the same as it does to action of the rabbit's own corpora. Pregnancy can be maintained to full term in the absence of the ovaries, and delivery can be prevented by continued administration of adequate amounts. It sensitizes the endometrium of the rat and the guinea pig so that deciduomata can be produced experimentally. In short it substitutes completely for the corpus luteum, except that for some types of response estrogen must be given

at the same time, i.e., some physiological responses attributed to action of the corpus luteum are in reality due to combined action of estrogen and progesterone.

Progesterone also has a specific action on the uterine muscle. It is well known from the experiments of Knaus[11] that the reactivity of the rabbit's uterus to pituitrin is materially changed during pseudopregnancy or pregnancy. If a segment of the uterus is removed from an animal in heat and suspended in a suitable saline bath, spontaneous contractions occur and can be recorded by means of a kymograph. If now a small amount of pituitrin is added, there is an immediate and prompt response, shown by a typical tetanic contraction. A similar response is, of course, obtained in the human uterus at the time of delivery when pituitrin is given. This sensitiveness to pituitrin in the sexually mature rabbit is always present when no corpora lutea are present in the ovaries. If functional corpora are present, as in pregnancy or pseudopregnancy, the uterus similarly studied in vitro, is not responsive to pituitrin. The uterus is refractory. This pituitrin-inhibition, as it is called, is due to the action of progesterone and can be produced experimentally by giving rabbits 1.0 mgm. of progesterone daily for five days (Makepeace, Corner and Allen).[12]

In vivo studies carried out by recording the uterine motility in anesthetized rabbits by means of an intrauterine balloon show too that progesterone has a quieting effect on the uterus. It has been shown that estrogen induces strong, rhythmical contractions and that progesterone brings about quiescence (Allen and Reynolds).[13] The effects are noticed rather quickly, indicating prompt absorption, even though the hormone is dissolved in an inert vegetable oil. It is this quieting effect on the myometrium which has led to the use of progesterone in dysmenorrhea, threatened abortion and premature labor.

The effects on the endometrium of the primates are of even greater interest because it has now been amply demonstrated that the cyclic changes which are known to occur in the corpus luteum phase of the cycle can be produced experimentally by the use of progesterone. The exact details of dose are not as well worked out as in the rabbit but several observers have produced premenstrual changes in both monkeys and women with progesterone.

The menstrual cycle of the primate is inseparably associated with the corpus luteum, whenever the cycle is ovulatory, but to complicate

matters, many cycles in monkeys are anovulatory and we have fairly good evidence that many types of abnormality in the human cycle are accompanied by and probably due to disturbances in the mechanism of ovulation. The types of cycles can be best explained by discussing the methods of inducing artificial menstruation.

Menstrual bleeding can be produced experimentally in both women and the lower primates by either of two mechanisms. If a castrated individual is given estrogen for a short period of time, say two or three weeks, the endometrium responds by moderate growth. If the hormone is then discontinued, vaginal bleeding similar to menstruation occurs, beginning about seven to ten days after the last injection. This bleeding is called estrogen-deprivation bleeding. The amount of estrogen necessary to produce this depends on the particular preparation used. With estradiol benzoate, for example, it requires 1.5 to 2.0 mgm. per week.

Before passing on to the second mechanism of producing bleeding, it may be well to dwell on the significance of this observation. Since bleeding can be produced with this one hormone alone, it becomes obvious that some menstrual cycles might actually occur because of this same mechanism. Follicles may grow, produce estrogens and then, without ovulation having occurred, undergo atresia. The estrogen level falls and bleeding occurs because of estrogen deprivation. This is obviously not a complete cycle because there has been no ovulation, hence, no corpus luteum, and therefore the endometrium does not progress to the premenstrual or secretory type. This type of cycle, called an anovulatory cycle was described first in the monkey by Corner. This was considered by many gynecologists, both in this country and in Europe, an interesting peculiarity of the monkey, but of no significance as far as the woman was concerned. Such is certainly no longer the case and many cycles in women are undoubtedly anovulatory. One of the first evidences of ovarian dysfunction is failure of ovulation.

Estrogen-deprivation is not the only method of producing menstruation experimentally. It was soon found that administration of progesterone would prevent estrogen deprivation bleeding. If a monkey is given estrogen, and then if progesterone is given, beginning as soon as the estrogen is stopped, no bleeding occurs. However, when the progesterone is discontinued typical bleeding occurs. Progesterone, therefore, prevents estrogen-deprivation bleeding, but its withdrawal leads to pro-

gesterone-deprivation bleeding. This means that bleeding can be due to two different types of endocrine change. Externally the bleeding is the same, but the type of endometrium from which the bleeding occurs is quite different in the two cases. In the estrin stimulated endometrium, bleeding occurs from an interval type of endometrium; whereas in the estrin and progesterone stimulated endometrium, bleeding occurs from a premenstrual endometrium.

A final way of producing bleeding probably nearly approximates the mechanism present in the normal ovulatory cycle. If a monkey be given an adequate amount of estrogen continuously, it is possible to produce menstrual bleeding simply by the administration of progesterone for a few days. Bleeding occurs two to three days after the last injection. This means that bleeding will occur whenever the progesterone level falls, regardless of the amount of estrogen present, within certain rather wide limits (Corner).[14]

An interesting variant of this experiment has been recently carried out in women by Zondek.[15] He has shown that administration of progesterone to a normal woman in the first half of the cycle leads to bleeding 48 to 72 hours after the last injection without at the same time necessarily preventing the appearance of the next normal menstrual period at the expected time. This only serves to emphasize the point that progesterone-deprivation is followed by bleeding provided the stimulation has been sufficient.

By way of confusing the issue it might be appropriate to point out what is already probably obvious to you, namely, that bleeding can occur from almost any sort of endometrium. The degree of development of the endometrium depends on the amount and duration of action of the two ovarian hormones but the bleeding occurs from hormonal deprivation (except possibly in hyperplasia), the stage of development of the endometrium being incidental and in no direct way related to the cause of the bleeding.

The final question is, what clinical uses can be made of the various physiological properties of progesterone?

Progesterone may be used in dysmenorrhea, the theory being that the pain is due to ischemia resulting from strong contractions of the uterus. Progesterone does relax the uterine muscle in both animals and humans and hence, should be beneficial in dysmenorrhea. The general opinion, I think, is that about one-half of the cases of dysmenorrhea are

benefited. My own experience has not been extensive, but in several patients there can be no doubt but that marked improvement was noted. The progesterone has to be given before the period has begun and I have had the best success when 1.0 to 2.0 mgm. was given intramuscularly on the last three days immediately preceding the flow. I have got the impression also that it is the progesterone given in the last 24 hours before the onset which produces the effect. Unfortunately the treatment is not curative in any sense of the word since the next period is usually as bad as ever.

Threatened abortion is, of course, theoretically the indication par excellence for progesterone. Excision of the corpus luteum of pregnancy results in abortion in most mammals (including the human in early pregnancy) and, experimentally, progesterone will maintain pregnancy normally following excision of the corpora. Transfer of this information to the human is not so justifiable, however, because there is very little evidence that abortion is necessarily due to corpus luteum deficiency. In many instances it may be and probably is due to corpus luteum deficiency but this is frequently due to the presence of a defective embryo in utero. The administration of progesterone to such a case, of course, might defeat the natural process of expelling the defective embryo. I have seen one such case where the abortion was prevented on two different occasions only to have a defective embryo expelled at the fourth month in which the placenta and membranes were intact but without a fetus. In case of a threatened abortion in which the bleeding is slight and the uterus of normal size and consistency for the period of amenorrhea, progesterone is, of course, indicated. It can do no harm and it may be beneficial.

The question of dose is paramount. In normal pregnancy at the third month 10 to 20 mgm. of pregnandiol are excreted daily (Venning).[16] If this be taken to indicate the amount of progesterone metabolized, it is obvious that 5 to 10 mgm. as a minimum should be given daily until the symptoms have subsided, i.e., for a week or so. It seems probable that some abortions may occur because the placenta does not begin elaborating sufficient progesterone quite soon enough, and if this be so, then progesterone given for a short time might be expected to give good results.

Habitual abortion is also considered an indication for progesterone. This is a rare condition and some of these cases will occasionally carry

a fetus to term after many previous miscarriages with no treatment. Many patients will have two or three spontaneous miscarriages only to have the following pregnancies progress normally. It is very difficult, therefore, to evaluate the beneficial results reported in the literature, especially since the doses used have usually not been large. In habitual abortion progesterone, if used at all, should be started almost as soon as pregnancy can be diagnosed and it should be continued probably to the fourth or fifth month, the reason for beginning early being that the fetus may fail to develop normally if the progesterone level is inadequate. In the rabbit progesterone deficiency in early pregnancy leads to defective development and early death of the embryos.

Functional bleeding is one condition worth special consideration. Amenorrhea or bimonthly bleeding usually do not impair the health, but continuous bleeding leads to considerable ill health, and rarely death has occurred from blood loss due to functional bleeding. The exact cause of the bleeding is not known. It is reasonably certain, however, that ovulation is not occurring and hence that progesterone is not acting. The use of pituitary hormones for this condition is based on the assumption that ovulation may be induced, and a normal cycle established. This can rarely be accomplished by this means. There is one other method of approaching the problem that is often successful. This involves the use of progesterone. As I mentioned earlier, progesterone has the property of preventing estrogen-deprivation bleeding and also of preventing the onset of normal menstrual bleeding, if given in adequate amount. It is logical, therefore, to try it, especially since continuous functional bleeding and hyperplasia are presumably associated with progesterone deficiency. There is an added reason. Some investigators believe that hyperplasia and the associated bleeding are due to hyperestrinism. If so, progesterone is the natural hormone to use because there is ample evidence indicating that progesterone reduces or at least alters the effect of estrogens.

We (Allen and Heckel)[17] have given progesterone to several adolescent girls with more or less continuous bleeding with rather uniform results. The general plan has been to give progesterone intramuscularly, 2 to 10 mgm. daily, for from five to ten days. Ordinarily the bleeding decreases markedly after the second and third dose but a small amount of brownish discharge may persist. When the injections are discontinued, the bleeding may recur within 48 to 72 hours and persist

for four or five days, resembling in every respect a slightly profuse menstrual flow. Bleeding does not invariably decrease when progesterone is given. Occasionally the spotting or even moderate bleeding may continue during the course of injections but usually cessation of injections is followed by increased bleeding. In every instance where this result has been obtained the flow has stopped completely after a few days. This bleeding is probably a true progesterone-deprivation bleeding. Bleeding may occasionally increase during the course of injections. The reason for this is not clear at present but there are so many peculiarities about bleeding that one can only record the observation and await the explanation. For example, I have seen bleeding occur in a castrated woman receiving estrogen daily, during a course of injections of progesterone, hence with no deprivation of either hormone. In other cases, usually when the smaller doses were given, the bleeding has stopped but there has been no recurrence as a result of the withdrawal of progesterone.

These results, by themselves, are of considerable interest but the subsequent course has been even more interesting. In most instances several fairly normal periods have followed the progesterone therapy. The first patient treated by this scheme was given crystalline progesterone in 1935. She was fifteen years old and had had continuous bleeding for two months. She was given 2.0 mgm. daily for five days and the bleeding stopped. Menstrual periods began about a month later and have been quite regular ever since. Another patient of seventeen years who had been bleeding daily for two years, was given 5 mgm. daily for six days. The bleeding stopped after the third injection. A copious menstrual period began two days after the last injection and lasted five days. During the next six months the periods were somewhat irregular but there were no prolonged periods and there was no episode of prolonged bleeding. I cite these two only as examples of what has occurred. In some cases there has been a recurrence of functional bleeding after several months of normal cycles, but the same beneficial results were obtained by a second course of progesterone.

The beneficial effects in functional bleeding from progesterone should not be permitted to obscure the fact that functional bleeding is a manifestation of ovarian dysfunction. As such it may indicate hypothyroidism and many patients with functional bleeding have been permanently relieved by the use of thyroid.

Amenorrhea, one of the most troublesome types of endocrine dysfunction when it is not amenable to thyroid extract and improved nutrition, provides another type of disturbance in which progesterone may be used. In view of the observation that the vicious cycle of continuous bleeding may frequently be broken by progesterone, I have tried it in several cases of amenorrhea in which there was no marked atrophy of the reproductive organs. In several cases the administration of 5 to 10 mgm. daily for six days was followed by menstrual bleeding, the onset being 48 to 72 hours after the last injection. One of these cases treated recently had had no menstrual periods for two years and had failed to menstruate following the use of equine chorionic gonadotropin, and human chorionic gonadotropin and had proved intolerant to thyroid extract. Two menstrual periods were induced by the use of progesterone, following which a normal period occurred. Another patient who had not menstruated for one and one-half years bled for four days after only three injections of progesterone. I cite these observations only to show that bleeding can be induced in amenorrheic individuals as a result of progesterone deprivation. Estrogen deprivation also is followed by bleeding in amenorrheic patients but it is practically never followed by normal cycles. It seems too much to hope that cycles produced by progesterone deprivation would be followed by normal periods but at least it can be no more of a failure than most of the other hormones that have been used.

There is one other compound closely related to progesterone which I shall mention. This compound is ethinyl testosterone (anhydro-hydroxy-progesterone, pregneninolone). It was prepared originally by Inhoffen and Hohlweg[18] in 1938 and was shown to be a compound with progesterone-like properties when given by mouth. This compound is far less active by mouth than is progesterone intramuscularly but it is much more active by mouth than is progesterone by mouth in the rabbit. In the guinea pig, however, Soderwall[19] (1940) has recently shown that progesterone and pregneninolone have about the same activity, the oral dose of either being about 20 times the injected dose of progesterone. This compound is also mildly estrogenic and mildly androgenic.

The indications for use of pregneninolone are the same as those for progesterone. It produces nausea occasionally but it is probably nontoxic in doses of even 100 to 200 mgm. per day for a period of two weeks or so. A recent report by Cohen and Stein[20] (1940) indicates that

it may be toxic in rats, hence caution must be observed in its use.

In conclusion it is proper to emphasize that the corpus luteum hormone has a firm place in the physiology of reproduction, and our appreciation of its many properties helps us to approach disturbances of ovarian function more rationally. It does not serve as a "cure-all" for any of the dysfunctions of the ovary but it is another tool which can be used in attempting to ascertain the cause of such disturbances. If used with that in mind the results are bound to be instructive.

REFERENCES

1. Fraenkel, L. Die Function des Corpus luteum, *Arch. f. Gynäk.*, 1903, *68:*438.
2. Loeb, L. Ueber die experimentelle Erzeugung von Knoten von Deciduagewebe in dem Uterus des Meerschweinchens nach stattgefundener Copulation, *Zentralbl. f. allg. Path.*, 1907, *18:*563.
3. Bouin, P. and Ancel, P. Recherches sur les fonctions du corps jaune gestatif. sur le determinisme de la préparation de l'utérus à la fixation de l'oeuf, *J. physiol. et path. gen.*, 1910, *12:*1.
4. Corner, G. W. Physiology of the corpus luteum; the effect of very early ablation of the corpus luteum upon embryos and uterus, *Am. J. Physiol.*, 1928, *86:*74.
5. Butenandt, A. Neuere Ergebnisse auf dem Gebiet der Sexualhormone, *Wien. klin. Wchnschr.*, 1934, *47:*934.
6. Slotta, K. H., Ruschig, H. and Fels, E. Reindarstellung der Hormone aus dem Corpus luteum, *Ber. d. deutsch. chem. Gesellsch.*, 1934, *67:*1270.
7. Allen, W. M. and Wintersteiner, O. Crystalline progestin, *Science*, 1934, *80:*190.
8. Hartmann, M. and Wettstein, A. Ein krystallisiertes Hormon aus Corpus luteum, *Helvet. chim. acta*, 1934, *17:*878.
9. Marrian, G. F. The chemistry of oestrin; preparation from urine and the separation from an unidentified solid alcohol, *Biochem. J.*, 1929, *23:*1090.
10. Butenandt, A. Über das Pregnandiol, einen neuen Sterin-Abkömmling aus Schwangeren-Harn, *Ber. d. deutsch. chem. Gesellsch.*, 1930, *63:*659.
11. Knaus, H. Zur Physiologie des Corpusluteum, *Arch. f. Gynäk.*, 1930, *140:*181; *141:*374; 395.
12. Makepeace, A. W., Corner, G. W. and Allen, W. M. The effect of progestin on the in vitro response of the rabbit's uterus to pituitrin, *Am. J. Physiol.*, 1936, *115:*376.
13. Allen, W. M. and Reynolds, S. R. M. Physiology of the corpus luteum; the comparative actions of crystalline progestin and crude progestin on uterine motility in unanesthetized rabbits, *Am. J. Obst. & Gynec.*, 1935, *30:*309.
14. Corner, G. W. The ovarian hormones and experimental menstruation, *Am. J. Obst. & Gynec.*, 1939, *38:*862.
15. Zondek, B. and Rozin, S. Production of uterine haemorrhage in the normal cycle and in amenorrhoea through progesterone, *J. Obst. & Gynec. Brit. Emp.*, 1938, *45:*918.
16. Venning, E. H. Further studies on the estimation of small amounts of sodium pregnanediol glucuronidate in the urine, *J. Biol. Chem.*, 1938, *126:*595.
17. Allen, W. M. and Heckel, G. P. *Unpublished observations.*
18. Inhoffen, H. H. and Hohlweg, W. Neue per os-wirksame weibliche Keimdrüsenhormon-Derivate: 17 Aethinyl-oestradiol und Pregnen-in-on-3-ol-17, *Naturwissenschaften*, 1938, *26:*96.
19. Soderwall, A. L. Induction of sexual receptivity in estrogen conditioned spayed female guinea pigs by orally administered progesterone and pregneninolone, *Endocrinology*, 1940, *27:*840.
20. Cohen, M. R. and Stein, I. F. Laboratory and clinical experience with oral pregneninolone, *Am. J. Obst. & Gynec.*, 1940, *40:*713.

CHEMICAL, PHYSIOLOGICAL AND CLINICAL ASPECTS OF THE ANDROGENS*

JOHN EAGER HOWARD

Associate in Medicine, The Johns Hopkins University School of Medicine

An extensive appreciation of the physiology of androgens dates from the chemical isolation of pure hormones, only a few years ago, 1933-35. In this brief period biochemists and physiologists have published a vast number of experimental observations on some sixty-odd pure chemical substances with androgenic properties; some prepared from sterols, some derived from animal tissues, still others derived from urinary extracts.[1,2] It may be well to pause for a moment to define the term androgen. Technically, an androgen is a substance which induces masculine qualities or characteristics. But what shall be our criterion of a masculine characteristic?

All sorts of ingenious tests have been devised for the measurement of the "male-producing" qualities or, in other words, the androgenicity of compounds. The two most common methods, as is well known, are based upon the effects of the test substance on either the internal genitalia (prostate and seminal vesicles) of spayed animals or on some external masculine organ (such as the comb) of spayed birds. The capon's comb-growth and the weight of the prostate of the spayed rat are the tests in most frequent use today. All sorts of modifications of these fundamental basic tests, however, are practiced. For example, somewhat different effects may be noted from variations in the method of administration of the substance to be tested, i.e., whether fed, injected or applied directly to the test organ by inunction. Further variables are found when esters are made of the test substances, due to alterations in the time of absorption. The same is true of variations of the medium in which the test substance is administered. The response of one animal species may be quite different from that of another; there may be different responses depending on the age of the animal, the season of the year and many other factors.[2]

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It is unnecessary to delve more deeply into these matters at this time; they are mentioned mainly to recall and emphasize how much care must be taken when we are attempting to interpret the results of any given experiment with androgenic substances.

As the result of experiments on lower animals, testosterone seemed the most logical androgenic steroid with which to furnish clinicians for extensive study in man. Because of its rapid absorption and also rapid destruction in the pure form, an ester was used and an oily medium, both of which retard absorption rates. The first extended clinical trials were, therefore, made with testosterone propionate in sesame oil, injected intramuscularly or subcutaneously. Since that time, some four or five years ago, various other methods of administration of testosterone have been tried clinically; among them the use of esters of testosterone other than the propionate, the use of free testosterone or its esters implanted in the form of hard pellets beneath the skin, administration of testosterone and esters by inunction, oral administration of methyl testosterone and, most recently, by means of absorption of testosterone or its esters dissolved in propylene glycol from mucous surfaces such as beneath the tongue.

Following the endocrine law that an organism is usually hypersensitive to a substance it lacks, eunuchs or hypogonad male patients were first selected for clinical trial, with the expectation, which has proved to be justified, that their responses to androgens would be more vigorous and spectacular than those of normal persons.[3] In most clinics a true eunuch is a rarity, and most studies have thus of necessity been performed on patients who are hypogonad for one reason or another—the degree of deficiency varying over rather wide limits, as might be expected. By restricting the study to patients long past the usual age of adolescence (say twenty-five years or over) without any evidence of puberty, one can with reasonable assurance feel that any maturation effects resulting from therapy may be attributed solely to the administration of the drug.

I think it may be fairly said that all workers in this field are now agreed that administration of testosterone *to this type of patient* results in certain definite changes to be described; differences of opinion being restricted to optimal dosage, method of administration or the ester to be used, etc.

The more dramatic and tangible physiological effects to which I

refer may be briefly set down as follows: enlargement of the phallus, scrotum, prostate and seminal vesicles with production of normal adult prostatic secretion; stimulation of pubic and axillary hair as well as that of the extremities, face and torso; cracking and deepening of the voice and enlargement of the larynx; an indefinable but definite change in the texture of the skin with more "life" and increased secretion of sebum.[4, 5, 6, 7, 8, 9] On the metabolic side, there is decreased urinary excretion of water, sodium, chloride, potassium, phosphorus and nitrogen, indicating probably active cellular proliferation with addition of true cellular mass.[10, 11] Retention of these substances is of greater magnitude than could reasonably be accounted for by the growth of the specifically "sexual" structures mentioned previously and is probably participated in by the muscles and internal organs such as the liver. Evidence of this is furnished in animal experiments,[12, 13] and we have been impressed with the increase in the muscles and proven strength in our patients. In addition to these tangible changes certain subjective effects are uniformly noted, namely: more vigor with less easy fatiguability, production of increased phallic sensitivity with more frequent erections, induction of the ability to have coitus with ejaculation and orgasm and, less tangible still, a general improvement in the sense of well being.[7, 14]

In the castrate and those with primary gonadal deficiency there is brought about reduction of the excess pituitary gonadotropic hormone.[15, 16] Increases in the basal metabolic rate have been noted, especially when large doses of testosterone have been used.[17] These are by no means all of the changes noted; some others will be mentioned later in the more detailed discussion of certain phenomena.

As previously mentioned, it may be fairly stated that all workers agree on the above effects when testosterone is given in adequate dosage to the hypogonad male; and, with some variation in degree of responses, this is true whether his hypogonadism is primary or secondary to pituitary deficiency.[10] Metabolic effects similar in kind though less in degree have also been noted when testosterone propionate was given to normal adult men and to two normal women.[11]

In the beginning of our own experiments with testosterone propionate in sesame oil given subcutaneously, we arbitrarily chose a dosage of 25 mgm. twice per week. This dosage seemed to work so well that we continued it over a period of eighteen months in practically all patients treated by this method.[5, 14] Allowing for certain deviations due to varia-

tions in the degree of gonadal insufficiency previously mentioned, the time-relationship and degree of responses elicited followed a surprisingly constant pattern. For example, the patients noted a subjective response of increased phallic sensitivity from the first to the eighth day after beginning therapy (average five days), vocal changes were noted from the twenty-first to the ninetieth day (average thirty days), definite enlargement of prostate and vesicles could be palpated from the eleventh to the sixtieth day (average thirty days), appreciable increase in pubic hair appeared from the thirtieth to the sixtieth day (average forty days), and measurable amounts of secretion could be recovered from prostatic massage from the thirtieth to the sixtieth day (average forty days).*

We have accordingly used this pattern of effects and time-relationships (which we shall hereinafter refer to as our "primary pattern of response") to evaluate the effectiveness of other androgenic preparations and other methods of administration.

We do not mean to infer that the injection of 25 mgm. testosterone propionate twice a week is the correct or optimal dose of this substance. As a matter of fact, were we to use this material today, we should advise slightly smaller doses of, say, 15 to 20 mgm., to be given three times per week to avoid the fluctuation of subjective effects which usually occurs when the material is administered at three or four day intervals. We shall discuss this later in dealing with optimal dosage.

The introduction into the subcutaneous tissues of crystalline testosterone pounded into hard pellets was next tried[14] according to the method of Deanesly.[18] The amount of the drug absorbed may be measured by periodic removal of the pellets and reweighing. One would naturally expect variations in the rate of absorption of such pellets depending on their size, surface area and on the degree of hardness. This is undoubtedly the case to a certain degree, but we have found a rather surprising uniformity in the absorption rate, at least until the pellets get very small. There is a vigorous foreign body reaction around the implanted pellets and a thick fibrous capsule is formed.[19] Within this capsule, in the case of testosterone, is a layer of thick gelatinous material looking not unlike pus, for which we at first mistook it. We have repeatedly cultured such material with sterile findings and examined it under the microscope where it looks like amorphous debris. We con-

* The time of noting these changes after beginning therapy is necessarily somewhat vague. We followed the patients as closely as we could, but it was obviously impossible to examine them daily. Since many of the patients were from other cities, we were forced to obtain these data from personal diaries.

cluded that the material consisted of testosterone, extracellular fluid and products of cellular breakdown.

This extra layer of amorphous liquid surrounding the pellet, rendering the surface area of absorption, of course, many times larger, and probably shrinking relatively little as the substance of the pellet is depleted, may perhaps be the explanation of the surprisingly uniform absorption rates of pellets of the same size and the small differences in absorption rates of pellets of different size. If pellets of pure testosterone are implanted of such size that they will yield 3 to 4 mgm. per day (a single pellet of 500-600 mgm. has been found to do this), clinical effects are obtained which correspond closely to our "primary pattern of response." It may be seen that this method of administration, if other factors are equal, effects a considerable saving of material.

We next tried pellets of testosterone propionate. It was found that, for a given pellet of the same weight and consistency, the rate of absorption of testosterone propionate is slightly lower than that of pure testosterone. This may be due to the fact that, although a similar fibrous capsule is found around the propionate pellet, there seems to be less amorphous fluid substance around the pellet; hence the capsule is closer to the pellet itself and there is a decidedly smaller surface area of the capsule. Such an observation is, of course, difficult to prove; but Jewett and Vest, who have implanted and removed all the pellets in our patients, feel that there is no doubt about its factuality.

We have found that if five pellets of 200 mgm. each of testosterone propionate—which will yield 3.5 to 5 mgm. per day into the circulation —are implanted, our clinical effects can be practically superimposed on our "primary pattern of response."

We have tried only one other ester of testosterone with pellet implantations and in only two cases. This is the dipropionate. In one instance we implanted two pellets weighing approximately 600 mgm. apiece and in the other, three pellets weighing approximately 200 mgm. apiece. In neither case, after several months' observation, could we detect any appreciable objective or subjective response; and on removal it was found that only minimal amounts of the material had been absorbed. (15 mgm. in the first case, 10 mgm. in the second). Striking also was the fact that practically no amorphous fluid lay around the pellets, the inner surface of the fibrous capsule apparently lying in direct contact with the pellets. This is just like pellets of desoxycorticosterone when removed.

Thorn tells me there is no surrounding fluid between the pellets and the capsule.[20] We feel that, if enough pellets of dipropionate were administered so that 4 to 5 mgm. could be absorbed per day, one would probably obtain good effects and perhaps over a period of two or three or more years. So far it has not been practical to test this hypothesis.

Despite the expressed preference of *every* patient who has tried other methods of testosterone administration mentioned, for the pellet form, it is not entirely free from disadvantages. Out of a series of 125 implants, seventeen have spontaneously sloughed out at varying periods of time. Three out of forty-one implants of testosterone have sloughed, fourteen out of eighty-four of testosterone propionate. Sometimes only one pellet out of the five implanted has been sloughed; in a single patient one pellet may slough at one month, another at three months, and the other three pellets successfully remain without the slightest evidence of irritation, to complete absorption. We have not been able to ascertain that the site of implantation, the depth of the site, the size of the pellet, the type of suture used or any other factor plays the determining role in this sloughing. In no instance has there been any evidence that infection played any role whatever. The tissue forming the capsules around these pellets has been removed and examined microscopically. Our pathologists tell us that there is simple foreign body reaction with many large multinucleated cells but no evidence whatever of any tendency to carcinogenesis.[19]

Administration of testosterone and its derivatives by inunction is practicable and perfectly efficacious, as judged by the experience of others.[21] We have had no personal experience with the method. We suggested its use to a few patients who preferred going twice a week to doctors for injections rather than the daily, time-consuming procedure of rubbing in the drug.

Methyl testosterone has been found in experimental animals far more effective by oral administration than any of the androgenic compounds so far tested clinically. Our own experience with this compound has thus far been too limited for me to state with any assurance its clinical characteristics, and no adequate reports of its use in human beings have come to my attention. Some of our previously untreated hypogonad cases, however, have followed quite closely our "primary pattern of response" when given doses of 25 mgm. of this drug per day; others, though the *direction* of response was similar in every instance, seemed to respond

more slowly, as if, in other words, higher dosage would have yielded prompter and more vigorous effects. In two instances, out of our series of thirteen cases, unpleasant side effects, quite similar to those often seen with diethyl stilbestrol, were encountered, necessitating discontinuance of methyl testosterone therapy. Good clinical response was at once attained on substituting pellet therapy in one instance, injection therapy in the other.

To come back to the matter of "optimal" dosage and adequate replacement therapy: If an amount of androgen is administered so as to bring about our "primary pattern of response," is this adequate or optimal? We must confess we do not know, but with the single exception of beard growth—which has never attained normal proportions in any of our forty-odd cases so far followed carefully—the patients are completely satisfied and have expressed the opinion that the replacement was subjectively "adequate."

One might use the urinary androgen excretion as a criterion of adequacy or inadequacy of treatment. With the doses we have used, our patients have in no instance reached the average normal range of 20 to 60 units per day as measured by Fleischmann's rat colchicine technique.[22] However, most of those tested have reached what we consider the lower limits of the wide normal variation.

We have recently assayed the urine of our treated patients for 17-ketosteroids* (using Fraser's modification of Callow's method).[23] Our patients have shown well below average normal figures, so that on this basis, too, we should perhaps judge our treatment as suboptimal.

Other workers have given far larger doses than ours and brought about high normal urinary androgen outputs tested biologically;[24, 25] but so far as we can see from their reports, their cases have responded clinically in a manner quite close to our primary pattern. Furthermore, urinary androgen titers are often very poor criteria for the clinical effectiveness of a dose. Dorfman and Hamilton's observations should be recalled in this regard.[25] By feeding 60 mgm. testosterone propionate to a hypogonad patient daily, they recovered in the urine androgen titers far higher than normal men ever show—yet with *little or no clinical effect on their patient.*

So for the present, at least, we plan to continue our present relatively low doses because of the great expense of the hormones and because,

* These assays were made by the ketosteroid laboratory of the Brady Urological Institute.

from the subjective standpoint, at least, we have felt our treatment to have been adequate.

The Fate of Androgens in the Body

We make brief mention of what is known of the fate in the body of administered androgens. As previously pointed out, one of the difficulties of androgen therapy has been the rapid destruction or inactivation of the material in vivo. The bulk of indirect evidence to date points to the liver as the site of this inactivation.[26]

Whether subcutaneously or cutaneously administered androgens enter the general circulation via the veins or the lymphatics is as yet unknown, so far as I am aware. It has been definitely shown, however, that pellets implanted in the spleen[26] are far less effective than those placed in areas in which the venous return does *not* go by way of the portal system to the liver. This bit of evidence would favor the hypothesis that absorption is via the veins.

Testosterone itself has never been isolated from the urine. Koch[2] and others have found that the androgenic activity of normal male urine resides largely in the form of androsterone and dehydroiso-androsterone, usually in roughly equal amounts by weight; almost all in the conjugated state, presumably salts of glycuronic acid.

The same authors found that when testosterone propionate was administered to hypogonad patients, the urinary bioassays of these patients were increased in such a degree that if they were in the form of equal parts of androsterone and dehydroiso-androsterone as in the normal, then approximately one-half the injected testosterone could be accounted for in the urine.[24] This ratio did not hold, however, for their one patient whose hypogonadism was primarily pituitary in origin, in whose urine far less than 50 per cent of injected testosterone could be accounted for.

Using 17-ketosteroid assays (which usually, but by no means invariably, run roughly parallel to the biological assays) of the urine of our patients on pellet therapy, we have also been able to account for approximately one-half the absorbed testosterone when calculated as milligrams of 17-ketosteroid excreted. On the other hand, only negligible increases of 17-ketosteroids have appeared in the urine when 25 and 50 mgm. of methyl testosterone have been given daily by mouth.

Other Uses of the Drug

The primary importance of any glandular hormone is obviously to replace a deficiency within the organism. But often we find glandular products useful in cases where no deficiency exists for their side effects or therapeutic purposes other than replacement, for example, the many uses to which adrenalin, insulin and thyroid extracts are put every day.

In Cushing's syndrome, Albright[27] has found a great increase in protein catabolism, and because of the known nitrogen retaining and tissue building properties of testosterone, has administered the drug to patients suffering with this disease. The results thus far have been surprisingly good from the patients' standpoint, with great increases in strength, lessening of fatigue and the resumption of normal utilization of nitrogenous foods. As might be expected, in some instances in females the clitoris has become enlarged, the beard increased, the voice deepened—but on the whole beneficial effects have seemed to far outweigh the detrimental.

Because of these nitrogen retaining, tissue building or "growth hormone-like" effects, we were tempted to give testosterone to male ateliotic (or symmetrical) dwarfs to observe its effects. Thus far it has been practical to do this in only one patient. One would hesitate to develop sexual maturation in a person to whom adult sexual appetites might prove more of a source of sorrow than otherwise. Just such a patient, however, begged us to accept him as a test object for this specific experiment. Methyl testosterone, for various reasons, was chosen in his case; and 25 mgm. has been taken orally per day for eight months. The result has been quite spectacular; in addition to rapid development of adult sexual attributes, this twenty-three year old dwarf has gained twenty-eight pounds, from seventy-two to one hundred pounds, has grown in height two inches, and his span has increased three inches.

Should one use the drug in cases of delayed puberty? Early in our experience we were hesitant to do so, first because of the pituitary tamponade effect with the possibility that sterility might result, and, second, for fear it might make the interstitial cells of the testes permanently "lazy" by taking over their function. But with more experience we now have no hesitation in using the drug in small doses (approximately one-half to two-thirds of that which would bring about primary pattern of response in adult hypogonad patients) in boys who

develop late. In every instance thus far we have found that on cessation of the drug puberty continued right along under its own stimulus. Webster's experience has been similar in this regard.[28] Had adolescence not further progressed after stopping the drug, it is likely that puberty would not have occurred at all and, therefore, the replacement would have had to be given eventually anyhow. It is not our purpose here to discuss the merits of using APL* or some similar stimulant instead of replacement gonadal hormone; our recent inclination has, however, been to favor the use of testosterone in these cases.

Effect on Gonads

In many of our hypogonad patients, the testes, though quite small, have seemed of normal consistency on palpation, and hence we assumed that the difficulty was not primarily testicular. (It should be mentioned here, however, that nearly all of the first twenty of our hypogonad cases had been given trial with APL with little or no response). In one or two instances, after *androgenic* therapy, measurements showed slight increases in testicular dimensions; but on the whole, we were able to detect no significant changes, as might be expected. In animals, removal of the hypophysis results in rapid degeneration of the spermatogenic elements; but if androgens are administered soon after hypophysectomy in certain animals, spermatogenic function is retained.[29, 30, 31, 32] In young animals, massive doses of androgens have been found to cause atrophy of the testes and permanent sterility,[33] probably by the pituitary depressant effect. In our patients, with our relatively much smaller dosage, no such effects have been observed. In fact, the experience of one patient is in quite the opposite direction. He was a moderately hypogonad man of thirty-two, with small phallus, scant pubescence, no beard and juvenile voice. He had been married eight years, no pregnancies having occurred. Prostatic secretion was negligible and in several massage specimens only a rare non-motile sperm was found (unfortunately, no ejaculate was studied prior to treatment). Since testosterone therapy was begun three years ago, two pregnancies have occurred, one resulting in miscarriage, the other in a normal child. Specimens of ejaculate now show normal sperm counts. We believe this to be an extremely important observation because one deduces that in these dosages it need not be feared that administration of testosterone

* Anterior pituitary-like substance, derived from the urine of pregnant women.

will cause sterility. Contrariwise, however, I do not believe that this experience should be used to advocate its indiscriminate use in sterility. This patient must be one in a very small percentage of sterile cases where the subnormal amount of available androgens was still able to maintain spermatogenic faculties, the additional androgens given then allowing increased spermatogenesis. This patient was the only one thus far in our series of forty-six cases in whom we have found any spermatozoa at any time.

In one of our earlier experiences with testosterone, the drug was given to a three year old boy, for other reasons, in doses of 30 mgm. twice per week.[5] Very marked advancement in bone age over a few months prompted us to study this phenomenon in our adult hypogonad patients. In nearly all patients, therefore, we have taken periodic x-rays, but to our surprise, found surprisingly *slow* advancement of their epiphyseal union, though in every instance followed over one year there has been some change.

Before closing I want to touch on one or two other uses for testosterone that have been suggested. With its use in prostatic hypertrophy we have personally had no experience whatever. From the reports that have come to our attention so far, the evidence seems so conflicting that we are dubious whether the administration of androgens alone will remove the necessity for operations in patients with prostatic hypertrophy.

Reports thus far on the use of testosterone in elderly men with so-called menopausal symptoms and depressions are also very confusing. Tangible evidence of cause and effect is uniformly lacking in the reports thus far, and this tends to leave one somewhat skeptical. However, certain experiences of our own have prompted us to feel that the matter deserves further study. A man of considerable prominence in public life, aged over seventy, received 25 mgm. testosterone propionate twice a week with great invigorating effect and some gain in weight, and he was altogether enthusiastic. Without the patient's knowledge, we substituted plain sesame oil ampoules (we labeled them plainly as containing the usual amount of testosterone) and the patient promptly returned to his pretreatment level. On resumption of the drug, the same subjective improvement occurred. In this, as well as in several other instances of this type, subjective benefit has been obtained without any manifestation of stimulation in the sexual sphere whatever. In other in-

stances in elderly males, however, we have noted marked sexual stimulation promptly, though the character of the drug was totally unknown to the patient. This whole subject, i.e., the use of androgens in old men, to our mind needs much more study.

For the impotent male, other than those whose condition is specifically lack of androgens, this type of therapy is utterly useless, as might be expected. Likewise, in our hands, no benefit has been derived when testosterone propionate is given to homosexuals in doses larger than those required to bring about our primary pattern of response in hypogonad patients.[3]

Gynecologists have recently been using testosterone and derivatives in certain types of ovarian dysfunction, with good results reported.[34] We have no personal experience with androgens in this type of case, and hazard the guess that the use of testosterone will be superseded by other substances when our knowledge of female steroid physiology is further clarified.

Such disjointed facts, ideas and suggestions as I have presented here are in no way presumed to have covered the field suggested in the title. Nor are these remarks intended to have laid down any set rules on such matters as whom to treat, how often, with what dosage or by what method. The whole subject is far too young for anyone, in my opinion, to do this at this time. These remarks have simply been the expression of some of my own opinions on a subject still far from well understood, gained from the experimental facts at hand and the clinical observations so far available. The theoretical material offered to you here may all have to be completely revised on the basis of yet unknown facts.

REFERENCES

1. Goldberg, M. W. Die Chemie der männlichen Sexualhormone, *Ergebn. d. Vitamin- u. Hormonforsch,* 1938, *1:*371.
2. Koch, F. C. The male sex hormones, *Physiol. Rev.,* 1937, *17:*153.
3. Rennie, T. A. C., Vest, S. A. and Howard, J. E. The use of testosterone propionate in impotence: clinical studies with male sex hormones, *South. M. J.,* 1939, *32:*1004.
4. Foss, G. L. Effect of testosterone propionate on a post-puberal eunuch, *Lancet,* 1937, *2:*1307.
5. Vest, S. A. and Howard, J. E. Clinical experiments with the use of male sex hormones; use of testosterone propionate in hypogonadism, *J. Urol.,* 1938, *40:*154.
6. Hamilton, J. B. Treatment of sexual underdevelopment with synthetic male hormone substance, *Endocrinology,* 1937, *21:*649.
7. Kenyon, A .T. The effect of testosterone propionate on the genitalia, prostate, secondary sex characters and body weight in eunuchoidism, *Endocrinology,* 1938, *23:*121.
8. McCullagh, E. P. Treatment of testicu-

lar deficiency with testosterone propionate, *J. A. M. A.*, 1939, *112:*1037.

9. Turner, H. H. The clinical use of synthetic male sex hormone, *Endocrinology*, 1939, *24:*763.
10. Kenyon, A. T. *et al.* The effect of testosterone proprionate on nitrogen, electrolyte, water and energy metabolism in eunuchoidism, *Endocrinology*, 1938, *23:*135.
11. Kenyon, A. T. *et al.* A comparative study of the metabolic effects of testosterone propionate in normal men and women and in eunuchoidism, *Endocrinology*, 1940, *26:*26.
12. Papanicolaou, G. N. and Falk, E. A. General muscular hypertrophy induced by androgenic hormone, *Science*, 1938, *87:*238.
13. Korenchevsky, V., Dennison, M. and Levy Simpson, S. Effects of water-soluble preparations of androsterone and androsterone-diol on castrated rats, *Biochem. J.*, 1935, *29:*2131.
14. Howard, J. E. and Vest, S. A. Clinical experiments with male sex hormones; further observations on testosterone propionate in adult hypogonadism and preliminary report on the implantation of testosterone, *Am. J. M. Sc.*, 1939, *198:*823.
15. McCullagh, D. R. and Walsh, E. L. Experimental hypertrophy and atrophy of the prostate gland, *Endocrinology*, 1935, *19:*466.
16. Nelson, W. O. and Gallagher, T. F. Studies on anterior hypophysis; effect of male hormone preparations upon anterior hypophyses of gonadectomized male and female rats, *Anat. Rec.*, 1935-36, *64:*129.
17. Kenyon, A. T. *Personal communication.*
18. Deanesly, R. and Parkes, A. S. Factors influencing the effectiveness of administered hormones, *Proc. Roy. Soc., London*, ser. B, 73, 1937-38, *124:*279.
19. Vest, S. A. and Howard, J. E. Clinical experiments with androgens; a method of implantation of crystalline testosterone, *J. A. M. A.*, 1939, *113:*1869.
20. Thorn, G. W. *Personal communication.*
21. Foss, G. L. Clinical administration of androgens; comparison of various methods, *Lancet*, 1939, *1:*502.
22. Fleischmann, W. The use of colchicine in the assay of androgens, *Endocrinology*, 1939, *25:*798.
23. Fraser, R. W. *et al.* The colorimetric assay of 17-ketosteroids in urine; a survey of the use of this test in endocrine investigation, diagnosis and therapy, *J. Clin. Endocrinology*, 1941, *1:*234.
24. Hoskins, W. H., Coffman, J. R., Koch, F. C. and Kenyon, A. T. The effect of testosterone propionate on the urinary excretion of androgens and estrogens in eunuchoidism, *Endocrinology*, 1939, *24:*702.
25. Dorfman, R. I. and Hamilton, J. B. Urinary excretion of androgenic substances after intramuscular and oral administration of testosterone propionate, *J. Clin. Investigation*, 1939, *18:*67.
26. Biskind, G. R. and Mark, J. The inactivation of testosterone propionate and estrone in rats, *Bull. Johns Hopkins Hosp.*, 1939, *65:*212.
27. Albright, F. *Personal communication.*
28. Webster, B. The treatment of hypogonadism in the adolescent male, *J. Pediat.*, 1938, *13:*847.
29. Walsh, E. L., Cuyler, W. K. and McCullagh, D. R. Physiologic maintenance of male sex glands; effect of androtin on hypophysectomized rats, *Am. J. Physiol.*, 1934, *107:*508.
30. Nelson, W. O. and Gallagher, T. F. Some effects of androgenic substances in the rat, *Science*, 1936, *84:*230.
31. Cutuly, E., McCullagh, D. R. and Cutuly, E. C. Effects of androgenic sterols in hypophysectomized and in castrated rats, *Am. J. Physiol.*, 1938, *121:*786.
32. Cutuly, E. and Cutuly, E. C. Observations on spermatogenesis in rats, *Endocrinology*, 1940, *26:*503.
33. Moore, C. R. and Price, D. Some effects of testosterone and testosterone propionate in the rat, *Anat. Rec.*, 1938, *71:*59.
34. Geist, S. H., Salmon, U. J., Gaines, J. A. and Walter, R. I. The biologic effects of androgen (testosterone propionate) in women, *J. A. M. A.*, 1940, *114:*1539.

SOME ASPECTS OF THE COMMON CONTAGIOUS DISEASES*

PHILIP MOEN STIMSON

Associate Professor of Clinical Pediatrics, Cornell University Medical College

EIGHT million each year is a reasoned estimate of the number of cases that actually occur in the United States of the eight diseases—measles and rubella, chickenpox and smallpox, diphtheria and scarlet fever, mumps and whooping cough. Only a million and a half of these are reported, but the average twenty-year-old American has had slightly more than three of these infections, or one each year for every six children, and there are 48 million children under the age of twenty-one in the United States. Hence these common contagious diseases are of great importance from the viewpoint of frequency of occurrence and loss of time, as well as because of crippling and death. In the last four years the reported death toll from these eight diseases has averaged a total of 11,600 a year. It is impossible to estimate how many people have been crippled in vision, hearing, or other functions by an attack of one or another of these infections or by complications thereof. Hence, the prevention, the diagnosis, and the treatment of these diseases will comprise the scope of this paper. In the time allowed one can stress only the less familiar and the more controversial aspects.

Prevention: Of these eight infectious diseases, three are caused by bacteria, and the other five presumably by viruses. Of the bacterial diseases—diphtheria, scarlet fever, and whooping cough—active immunization is obtainable by the use of vaccines in all three diseases. For diphtheria it is universally advocated and a modified toxin is used. For scarlet fever it is widely advocated in theory, but for certain types of people only, and not as a routine public health procedure and an unmodified toxin can be used. For whooping cough it is not yet advocated by public health authorities, but many practicing doctors advise it, espe-

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From the Department of Pediatrics, Cornell University Medical College.

cially for infants, and bacterial protein extracts are used. There is now much evidence to show that the Sauer pertussis vaccine is worth while; perhaps the most convincing of recent results being that of Garvan, who compared the incidence of whooping cough the last four years in Cleveland, where only about 10 per cent of the children have received the Sauer vaccine, with the incidence of the disease in the neighboring Shaker Heights, where possibly 75 per cent have been inoculated with this material. Use of the vaccine was started in 1934. In the four years beginning 1936, the yearly average of whooping cough in Shaker Heights showed a decrease of roughly 83 per cent (83.4) from the preceding seven year period, while the corresponding decrease in Cleveland was but 11 (10.7) per cent. In other words, where the majority of the children had received the vaccine, whooping cough showed a more than proportional decrease. Even when vaccine fails to protect, Kendrick and others have shown that pertussis attacks occurring in vaccinated children are definitely less severe than those in control groups. The vaccine can now be obtained in strengths of 15 and 20 billion bacteria per cubic centimeter, and the total dosage should reach 100 billion. After this has been given, preferably at five months of age, some advocate a small "refresher" injection of 1 cc. each year through early childhood.

At the present time it is quite universally taken for granted that all children should be immunized against diphtheria, but attention should be called also to the need for protection of adults. In the last decade and a half since Zingher published statistics about diphtheria immunity as shown by the Schick test, including the finding that 80 per cent of young adults were immune, there has been a distinct decrease of this accidental active immunity presumably due to the lessened likelihood of inoculation by exposure, and this year Thelander reported only 40 per cent of young adults as being immune. Correspondingly, there has been an increase in the proportion of cases of diphtheria that occur in persons twenty years old or over, so that in the last five years in New York City, one-fifth of the cases have been in adults, with a mortality of 4.2 per cent. Certain types of men, particularly the homeless derelict, are apt not to receive adequate treatment in the first few days of their diphtheria, and the mortality for such cases is very high, 50 per cent in one small series of six.

Two properly given injections of alum-precipitated toxoid at in-

tervals of a month apparently have as high an immunizing power as three injections of plain toxoid, but inasmuch as the alum-precipitated toxoid exists in suspension and requires a larger caliber needle and special care for proper injection, the plain toxoid is probably the more satisfactory preparation for the average practitioner's use. The dosage under six years of age is 0.5 cc. for the first injection and then 1.0 cc. for the other two at intervals of three or four weeks; while after that age the first dose should be only 0.25 cc. For children who receive this immunization in the first year or two of life, a further small injection of 0.1 or 0.2 cc. of toxoid is advocated at the time of entering school at six years of age by the New York City Department of Health.

Schick tests done in the presence of some other acute disease than diphtheria, such as in patients suffering from pneumonia, measles, or poliomyelitis, may give a bullous reaction which Fischer and his coworkers have recently shown does not necessarily mean susceptibility to diphtheria. In some cases a repetition of the Schick test after the patient has recovered from his acute infection has given negative results. Apparently bullous Schick tests are not found in normal healthy children. Incidentally, the Schick relapse rate is "three times higher in children who have had diphtheria than in children who have been actively immunized."

For scarlet fever a properly performed and accurately judged Dick test is evidence of immunity when negative. Klein's work on the immunization of affiliated nurses at the Willard Parker Hospital has been most illuminating on this point. Prior to coming to the hospital for their three months' course of training in the care of contagious diseases, the nurses are supposed to have negative Dick tests, but up to January, 1937, 2.9 per cent of over a thousand of these nurses contracted scarlet fever during their stay. The hospital thereafter undertook to Dick test each nurse on arrival, and since then no case of scarlet fever has occurred among 1348 nurses known to be Dick negative. During this period, eleven cases have occurred among nurses and interns who were not Dick negative.

In general, because of the prevailing mildness of scarlet fever, because of the large amount of toxin necessary to get a durable immunity, and because of the frequency of unpleasant reactions to the injections, immunization with scarlet fever toxin is not usually recommended for all children, but rather for children in such institutions as orphan asy-

lums where scarlet fever occurs frequently; also for members of a family where there is scarlet fever, and for doctors and nurses in positions of special exposure.

Passive immunization by means of the administration of serum is well-established for two of these three bacterial diseases, diphtheria and scarlet fever, and as for the third, whooping cough, Bradford, McGuinness and their co-workers have recently stated that convalescent blood serum in doses of 10 to 20 cc., when injected into exposed infants, confers a certain degree of protection for a limited period of possibly three weeks, as does also hyperimmune serum. This protection is particularly important since infants up to five months of age do not respond well to active immunization procedures, nor do young infants inherit an immunity to whooping cough. In fact, at the present time this disease kills more babies than diphtheria, scarlet fever, and measles combined, and the newly established protective value of immune serum is of great importance.

The other five of these contagious diseases, to wit, measles, rubella, chickenpox, smallpox, and mumps, are all presumably due to infection with specific viruses, and as such have several factors in common.

Factor I: virus diseases in man are for the most part more easily communicable than the bacterial diseases, of the latter whooping cough being a notable exception.

Factor II: viruses cause diseases which as a rule are followed by a lasting immunity, the immunity probably being both cellular and humoral. Herpes of the lips and influenza are probably notable exceptions to this. The late Hans Zinsser has noted that in some of the virus diseases, especially measles and poliomyelitis, the initial immunity may perhaps be constantly reinforced by successive exposures.

Factor III: as to chemotherapy, according to Carey and others, there is sufficient evidence to conclude that no sulfonamide compound has yet been found which has any effect on infections caused by a filterable virus.

Factor IV: passive immunization with serum might be expected to have some value in those virus diseases in which the virus is generally distributed by the circulation. This has been proved to be the case in measles and apparently also in mumps, but not yet in chickenpox and smallpox, although both are quite certainly also infections in which the virus circulates in the blood. On the other hand, to quote Zinsser again,

one cannot expect much prophylactic value in infections such as rabies, encephalitic processes, and poliomyelitis in which the virus travels centripetally along nerve trunks. Virus infections being intracellular processes, serum injection after the virus has penetrated into susceptible cells, has not proven of preventive or therapeutic value.

Factor V: active immunization against these and other virus diseases of man has not as yet been obtained by vaccination with dead or inactive material. Zinsser called this a field still in its infancy. It is of course well known that the virus used for vaccination against smallpox for the past century and a half is an active one modified by passage through calves or, more recently, through chick embryo tissue.

Following such vaccination, no matter how carried out, the virus of vaccinia is distributed generally throughout the body, going from the site of vaccination to the nearer lymph nodes, whence it enters the circulation. Ordinarily it does not produce any lesions in the tissues nor any symptoms except fever and usually some inflammation of the regional lymph nodes. In exceptional cases the virus can cause an encephalitis with tissue change and corresponding symptoms. The secretions of the nasopharynx have been shown to contain virus on the fourth and fifth days after vaccination; therefore, a recently vaccinated person by mere exposure can conceivably cross-infect with vaccinia a susceptible person, and by skin to skin contact can certainly infect such unusually susceptible individuals as children with chronic skin diseases. Even in normal individuals, a routine vaccination may result in a generalized vaccinia but where there is a preëxisting skin trouble, as in eczematous babies, vaccination, intentionally or accidentally accomplished, may cause an unusually dangerous condition known as eczema vaccinata, frequently terminating fatally. It is well, therefore, not only to postpone vaccinating children with chronic skin diseases until the eruption has been thoroughly cured, but it is further highly desirable to isolate eczematous children from recently vaccinated persons.

Before leaving the subject of immunization, mention will be made of two research activities that promise further advances in the prevention of disease. First, Rake and Shaffer, Stokes and O'Neil have recently produced a measles vaccine that is prepared by growing the virus on the chorioallantoic membrane of a developing chick embryo, apparently thereby modifying its virulence for mankind. Experimental inoculation of children with this vaccine produced little or no illness but at

the same time stimulated the production of at least partial protection against the unmodified virus. This work is of great promise.

Second, last June at the convention of the American Medical Association, Gladys Dick described a preparation of scarlatinal toxin that could be given in pill form by mouth for immunization. At the present time the material is available for research purposes only.

Diagnosis: The etiological and clinical manifestations of these infections are all so well-known that at this time it would seem well to call attention only to a few points of special concern. Cases of measles can be expected in great number in New York City at least this coming winter and spring. In large cities it is a disease usually marked by biennial epidemics, with occasional breakstep years in which an epidemic occurs on a second successive year. New York City has just experienced the other type of breakstep year, the last two springs having been unusually free from the disease. A new generation of little children is with us, and New York must expect perhaps 40,000 cases before July.

Unlike scarlet fever, measles is not spread by its complications, and it need not be isolated after five days from the appearance of the rash. The blood of a person incubating measles, if used for transfusion, can transmit the disease to the recipient at least during the latter half of the incubation period, perhaps even earlier. It is to be hoped that none of the hundreds of people who are donating blood plasma to be sent to England is incubating that disease. The usual sterility tests do not guard against that, at present, remote possibility. However, in *pooled* plasma there are probably enough antibodies to neutralize any possible virus present in a single blood.

In little children measles is frequently confused with rubella and with roseola infantum. The probability in uncertain cases is in favor of a diagnosis of roseola. It should be remembered that rubella (often popularly called German measles) is rare except in the presence of an epidemic, and isolated cases, particularly in little children, are quite uncommon. On the other hand, roseola infantum almost always occurs in two- and three-year olds. Its manifestations are characterized by about three days of unexplainable fever after which there is usually a fairly rapid return of the temperature to normal, followed by the development of a morbilliform or measles-like eruption, which appears first on the body and sometimes spreads to the extremities and the sides of the face. There are no Koplik spots and no appreciable conjunctivitis,

coryza, or cough. The rash lasts only a day or two, and is not followed by pigmentation. The blood shows a decrease in the number of granulocytes. Except for its preliminary fever, the disease is very much like modified measles. However, it is not a result of exposure to measles, and usually occurs in sporadic cases without known causative or subsequent cases.

About chickenpox, several instances have been noted recently in which a case of herpes zoster has been followed 14 to 16 days later by one or more cases of typical chickenpox. It is very unusual, however, to see the reverse, that is, herpes zoster follow a case of chickenpox. A connection between these diseases has long been suspected, but the etiological relationship is still unproved.

For a rapid diagnosis of diphtheria there has been quite a little in the literature about the use of a 2 per cent aqueous solution of potassium tellurite. The liquid is used for swabbing suspicious exudates, and in 15 to 30 minutes a black discoloration of the false membrane and the appearance of the odor of garlic are said to indicate a diphtheritic process. However, false positives appear on any tongue and occasionally in non-diphtheritic lesions, so that any positive test requires bacteriological or clinical confirmation. A negative test suggests but does not prove the absence of diphtheria bacilli. In general the tellurite test is hardly worth doing.

A further point in the differential diagnosis of diphtheria may be mentioned. Diphtheria does not cause erosion or ulceration, but rather a piling up of necrotic confluent material on an inflamed surface. When erosion can be detected, one should suspect syphilis, if the lesion is comparatively painless; or, if painful, an angina due to the Vincent microörganisms; and if the ulcerative pharyngitis is accompanied by much prostration, agranulocytosis should be suspected.

For the diagnosis of diphtheritic myocardial involvement and its after care, the electrocardiogram is of great value. Besides at times revealing delay in conduction time, an entity usually accompanied by such other clinical manifestations of toxicity that an electrical recording is not necessary for diagnosing heart trouble, the electrocardiogram may reveal only an inversion of the T wave. Burkhardt has shown that this is enough indication for keeping a diphtheria patient in bed until the abnormality in the tracing has cleared up, sometimes as long as two months. A diphtheritic myocarditis that does not terminate fatally does

not result in a crippled heart, however, but goes on to eventual complete recovery.

Mumps is a far more important disease from the public health and military standpoints than is generally understood. Throughout the United States Army in the World War one out of every twenty white men and one out of every six colored men had an attack of the disease; and in four camps, all in the far South, over 20 per cent of the soldiers at one time or another during their stay at the camp had mumps. Haven Emerson has stated that in terms of sick wastage and measured by the number of days lost from military service on account of sickness, mumps was the most important disease in the American Expeditionary Force; and Parran has added that next to the venereal diseases, mumps is the most disabling of the acute infections among the recruits. It is my belief that neither authority considered the respiratory infections for which five times as many soldiers were hospitalized as for mumps. Even so, the army lost 3,884,147 hospital days because of this disease, a number exceeded only slightly by that of the days lost due to gonorrhea. Apparently the portal of entry for the specific filterable virus of mumps is by the nose and throat, following which there is a general infection, probably of the blood stream rather than a strictly localized disease. According to Gordon, following the general infection the virus maintains a marked predilection for glandular structure, of which the parotid glands are most often the first affected. However, the other manifestations of mumps, such as orchitis, pancreatitis, and encephalitis, may occur as independent processes preceding involvement of the salivary glands, accompanying it, following it, or occurring without such involvement, and these manifestations should be considered part of the disease rather than complications.

Those lesions which are accompanied by pressure, such as orchitis hemmed in by the tunica albuginea, and encephalitis hemmed in by the cranium, are associated with the most fever, and also are most definitely helped by the relief of pressure. Wesselhoeft strongly advocates early incision of the tunica albuginea in marked cases of orchitis to relieve the intense pain, to shorten the duration of the swelling, and to diminish the extent of atrophy. Incidentally, sterility from mumps is exceedingly rare because only a small proportion of cases of orchitis are bilateral, 16 per cent according to one estimate, and even then it is rare for both glands to lose all function.

Encephalitis is probably far more common in mumps than has been suspected before the last year or two. It may be latent, consisting only of an infiltration of lymphocytes into the spinal fluid, as disclosed by a lumbar puncture, without any clinical manifestations whatsoever to suggest the encephalitis. On the other hand, there may be mild evidences of headache and stiff neck or more definite manifestations of meningeal involvement, with or without those indicating an encephalitis. Serious cases are quite exceptional. The usual duration of symptoms and signs of a mumps encephalitis is not more than three or four days and sequelae are quite rare. Incidentally, the encephalitides following which such sequelae as character change are most common, are the epidemic type, those complicating measles and whooping cough, and that due to lead poisoning.

Treatment: In presenting a discussion of advances that have been made in recent years in the treatment of various of these contagious diseases, one must first mention the difficulties involved in evaluating any new therapeutic remedy or procedure. Most of these diseases are so variable in their clinical manifestations and courses, not only from year to year but from case to case, that unless a remedy is tried on a large series of patients during a number of different years, the results being compared with a similar series of coincident control cases, one can only conjecture whether the remedy is beneficial or not.

Many factors can contribute to the cure of the patient besides a particular drug or serum. The violence of an epidemic, the kind of weather at the time of the epidemic, the coincidence of other infections, particularly upper respiratory infections, the hospital facilities available and particularly the possibilities of adequate individual isolation, and the skillfulness of medical and nursing attention generally, all provide factors of variability. For instance, in the last ten years at the Willard Parker Hospital the actual methods of treating whooping cough have varied little if at all from year to year. Yet in this decade the annual mortality of whooping cough patients at the hospital has ranged from 8.8 per cent in 1931 to 2.1 per cent in 1939, a variation of over four to one.

As to the management of contagious diseases, in recent years it has become almost universal in hospitals specializing in these maladies to apply individual isolation to each case of each disease. It has been shown that by protecting patients from the illnesses and complications

which others may be suffering in the same hospital or the same ward, cross infections with second diseases may be cut down, complications due to secondary infections may be diminished, and the average length of stay in the hospital may be shortened. On the other hand, when there is overcrowding and a shortage of nurses, as was the case at the Willard Parker Hospital last spring, when with a capacity of 420 patients there was an average of over 500 for about two months, then isolation technique must be given up and there is certain to be, and in this instance there was, an increase in cross infections and in complications.

Isolation technique is founded on the theory that infection is not air-borne, other than by cough droplets, and then only for perhaps five feet. But it has been shown by several workers in England that streptococci can be isolated from the dust of a room 24 hours after a patient has been removed from that room, and it is quite generally believed that both chickenpox and smallpox may be definitely air-borne, perhaps also measles and whooping cough.

Nevertheless, aseptic technique, founded on the principle that contagion is spread by direct or indirect contact only, remains the chief means by which hospital cross-infections can be restricted. Much work has been done by several groups of investigators, such as McKhann, Steeger, and Long at the Children's Hospital in Boston, on the use of the ultraviolet ray in the control of hospital infections, with very encouraging results. The injection of parental blood serum into every child on admission into a general pediatric ward has been advocated by Barenberg and his co-workers, while Fischer and Raue have similarly used placental extracts. It is known that pooled placental extracts will neutralize diphtheria toxin and poliomyelitis virus, will blanche scarlet fever rashes and protect against measles; and adult sera, particularly if pooled, will probably do as much. However, chickenpox continues to be the bane of crowded hospitals. Although almost never a menace to life in itself, it can prove a dangerously complicating factor when there is sepsis or marasmus, and there is no preventive for this extremely contagious disease.

Chickenpox is now usually treated with special emphasis on cleanliness. Patients are given careful daily baths without rubbing, and are blotted with towels rather than wiped, so as not to break the blebs of the young lesions. Any irritation of the skin is carefully avoided, and from any patient with chickenpox, plaster casts and adhesive plaster

should be removed promptly so as to avoid pressure on the skin and possible gangrenous areas or confluent eruptions.

Of the other exanthemata, scarlet fever is particularly variable so that any therapeutic agent is difficult to evaluate. Whereas in recent years virulent forms of the disease are said to have occurred in the Balkans, with a mortality of 10 to 25 per cent, over seven hundred cases of this malady were discharged in 1940 from the Willard Parker Hospital before a patient died there of scarlet fever, and for the past several years in New York City the mortality for this disease has been but a small fraction of one per cent. Two valuable therapeutic sera are at our disposal for the treatment of toxic cases. Human convalescent serum given intravenously in doses of 40 to 100 cc. is remarkably effective in neutralizing the toxic manifestations of the disease within 24 to 48 hours' time, and practically invariably without unpleasant reactions. Of horse sera, two manufacturers have recently made preparations of such refinement that the incidence of serum reactions following their administration has been cut well below 10 per cent. Therapeutic results are comparable to those obtained with human serum, and the cost is very much lower. While chemotherapy has as yet proved of little if any value in the treatment of scarlet fever itself, the administration of sulfanilamide during the acute stages has in some series seemed to lessen materially the incidence of complications, but this result has not been obtained universally.

The work of Allison and Brown in England has shown that when cases of scarlet fever are exposed to each other, the patients are apt to infect each other with additional strains of the scarlatinal streptococcus, and most of the complications that occur in the third week or later are due to these cross infections. This may explain why sulfanilamide, which has no apparent effect against the streptococcus of scarlet fever, may in some instances fail to prevent complications, while in other situations, perhaps where the secondary invaders are other microörganisms, it may prove quite protective or therapeutically beneficial.

In the treatment of measles there have been interesting developments. Kohn and his associates have given large doses of convalescent serum, 40 to 50 cc., intravenously, to patients developing measles but still in the preëruptive stage, and have apparently materially lessened the severity of the period of eruption. This may prove of considerable importance for patients already suffering from some such condition as pneumonia,

when the complication of an oncoming measles is discovered. This use of serum is the only instance in the virus diseases of man wherein a therapeutic serum, administered after the onset of evidences of the virus infection, is of any apparent value. Even so, in these measles cases the serum must be given at least 24 hours before the appearance of the rash to accomplish even partial modification of the oncoming disease.

As sometimes is the case in scarlet fever, measles patients frequently may be protected from the complications due to secondary infections with streptococci by the administration of sulfanilamide, a procedure which may prove useful in hospital services, but which probably will not become generally used in private practice because of the very low incidence of complications of measles in private homes, particularly of the better class. The pneumonias which complicate measles have proved in a large percentage of cases to be responsive to chemotherapy. Most of these pneumonias are due either to streptococci or pneumococci or to mixed infections. In some, the causative factor is thought to be some kind of filterable virus because, among other reasons, pneumonias are occasionally found complicating measles in which no pneumococci can be found nor a predominating number of streptococci, and for which the sulfonamides do not appear to be beneficial.

Whooping cough pneumonias are given such specific treatment as is indicated from the results of the cultures. Pneumococci are frequently found, and specific serotherapy together with sulfapyridine is helpful for these cases. However, many of the pneumonias in whooping cough are due to the pertussis bacilli themselves, perhaps others to filterable viruses, and in general chemotherapy has not proved as efficacious in the pneumonias of whooping cough as in those of measles.

Habel and Lucchesi of Philadelphia have shown that the convulsions of whooping cough which have so frequently proved fatal in infancy, are usually due to an anoxemia of the brain, secondary to the cyanosis caused by the paroxysms and by bronchopneumonia. Treatment with oxygen and transfusions has in their hands materially lowered the mortality following the convulsions of whooping cough.

Various vaccines have been recommended for the treatment of early whooping cough cases. The detoxified pertussis antigen in five to six doses given one a day or on alternate days, has seemed to mitigate the ensuing disease in some series, but not in others. As to the Krueger undenatured bacterial antigen, Stallings of California has summarized a

number of reports to indicate that daily injections, repeated over 10 to 14 days, have apparently brought considerable relief from troublesome paroxysms for many hours following each dose, but actual curative effects from the use of this vaccine are doubted by many, and the procedure is both expensive and disturbing to the patient.

As to diphtheria, the mainstay of treatment continues to be the early administration of adequate doses of diphtheria antitoxin. An injection of not less than 10,000 units intramuscularly is given for the mildest cases, and it is believed at Willard Parker that doses larger than 25,000 units intravenously and 25,000 units intramuscularly are never necessary. Other hospitals, particularly abroad, report that they occasionally give over 100,000 units to some patients.

Following the work of Schwentker and Noel at Johns Hopkins, toxic cases of diphtheria are usually given intravenously considerable quantities of 5 or 10 per cent solutions of glucose. The liver's ability to store glycogen is materially damaged by diphtheria toxin, and glucose by vein has seemed of marked benefit in clearing up the toxic manifestations. Cases of laryngeal diphtheria are usually treated so successfully by aspiration that intubation for diphtheria is now a comparative rarity. Diphtheria itself is becoming an uncommon disease, and for many months this past winter there were admitted to the diphtheria service more patients suffering from streptococcus or staphylococcus laryngotracheobronchitis than from diphtheria.

The treatment of these non-diphtheritic laryngeal cases has changed somewhat in the past several months. It was formerly believed that in the presence of a severe streptococcus infection, operative interference with aspiration, intubation, or tracheotomy was contraindicated because there was little or no exudate to remove by suction, but on the other hand there was extensive inflammation, edema, and swelling of the mucous membranes which were aggravated by any mechanical interference. In the past year or two a number of these severe cases have been treated in comparatively early stages with tracheotomy as the only surgical procedure, and something over 70 per cent of the cases severe enough to require an operation have been saved.

Serum reactions are less common than they formerly were, due to the more refined methods of preparing serum. As yet there has been comparatively little experience with the prevention and treatment of these reactions by the use of histaminase. At The New York Academy

of Medicine on April 16, last, Grace Roth from the Mayo Clinic reported confirmation of the work of Foshey and Hagebusch, which showed that five-unit enteric-coated tablets of histaminase, when given by mouth, tend both to prevent and to mitigate serum reactions. Further confirmation is not yet available.

Some doctors believe that if a person is markedly sensitive to horse serum, as shown by positive intradermal and eye tests, he cannot safely be given therapeutic doses of serum. The case is probably very rare indeed to which serum cannot be administered if proper precautions are taken. An unemployed negro longshoreman was recently admitted to the Willard Parker Hospital with an extensive pharyngeal diphtheria of three days' duration. His intradermal and eye tests for serum sensitization were both positive. A tourniquet was placed loosely high around one thigh and 0.1 cc. of serum was injected subcutaneously into the mid-thigh, accompanied by 3 minims of adrenalin. Each half hour a larger dose was given until at the end of nine doses a total of 35,000 units had been administered, part subcutaneously and part intramuscularly, each injection being accompanied by the administration of 3 minims of adrenalin, and both legs being eventually used. There was no immediate reaction to the serum, and the following day the diphtheritic process had largely disappeared.

Incidentally, for a patient's comfort, the serum should not be given in the outer or lateral aspect of the thigh, the fascia lata preventing swelling as a result of the injection, and causing the patient undue discomfort. Most patients prefer to receive a large amount of serum in the gluteal muscles.

Before closing I will add a paragraph or two about poliomyelitis. Of new information about the disease there is little that is not negative. While the virus in scattered instances can be found in the secretions of the nose and throat, it is found more commonly in the stools; and in the presence of an epidemic of the disease, it can be identified even in the stools of apparently healthy persons. It has been detected more readily in the stools of cases of the usually unrecognized abortive type than in paralytic patients. Virus can exist in large amounts in sewage in which it can be transmitted at least an eighth of a mile.

As Paul said a week ago in New York,* we do not know how the virus enters the body, nor how to prevent its entering. Because the nasal

* Paul, J. R. Poliomyelitis. *Bull. New York Acad. Med.*, 1941, *17*:259.

bulbs are so seldom involved, more and more students of the disease are coming to believe that a nasopharyngeal portal of entry is unusual rather than the rule, and that the disease is perhaps transmitted by a number of channels, as by direct contact with an infected person or by such other means as infected food or water. Paul mentioned the possibility that there may be other than human hosts or reservoirs.

Thus, there is little new to recommend for the prevention of the disease. In epidemic times, personal hygiene should be stressed as well as the avoidance of excessive fatigue and of unnecessary exposure to any illness. Milk should be pasteurized and drinking water boiled. In order to keep water out of the nose, swimming might well be omitted particularly wherever there is a possibility of contamination with sewage. The removal of tonsils and adenoids should be postponed, in fact, any procedure that might traumatize the nasopharynx should be avoided. Psychologically and practically, it is well in any given community that recommended regulations should be made uniform and authoritative by the health officers.

As for treatment, complete rest is almost the whole story. In the presence of an epidemic, any child with only a minor illness such as a slight cold or an alimentary disturbance, should be considered a presumptive abortive or preparalytic case and be given prolonged bed rest with a very minimum of handling. In more definite cases, parents should be made to understand that absolute rest is so vital that even a transfer to a hospital might be harmful, except of course where the use of a respirator is indicated. Many cases might be cited where a patient continued in normal activity with what seemed to be a minor illness, and then developed extensive paralysis. Paul related several of these last week, and we all can remember vivid instances.

When a diagnosis is definite and muscle weakness has appeared, then the patient should be put in a neutral position with no muscles stretched or under tension, and should be protected from all unnecessary handling or other disturbance. At the Willard Parker Hospital no serum is used. If a patient seems toxic or in any way seriously involved, he is given a 10 per cent glucose solution intravenously. This past summer we have experimented with massive doses of thiamin chloride intravenously and in the twelve or fourteen cases in which it was used, have thought we obtained astonishingly rapid recoveries of those muscles which on admission showed only weakness, not complete paralysis.

There were no control cases, so nothing has been proved. However, we shall probably try it another season.

In summary, we have noted how serums are curative for some bacterial diseases, and chemicals are for many. Last spring, at The New York Academy of Medicine, Perrin Long pointed out that about 75 per cent of bacterial infections now respond to chemotherapy, notable exceptions being whooping cough, typhoid fever, tuberculosis, and common colds. It is greatly to be hoped and rather confidently to be expected, that for these remaining bacterial diseases the next few years will see the discovery of specific remedies. The virus diseases of man are still without either a specific curative serum or a therapeutic chemical. Perhaps for these infections also therapeutic agents of great efficiency may be revealed.

THE MARRIAGE OF MEDICINE AND CIVIL GOVERNMENT*

HAVEN EMERSON

It is for me a happy accident of the passing years and of chance circumstance that I have been privileged to attend as member of the official family of our community both the golden, and this, the diamond wedding anniversary of a marriage of medicine and government which has produced enduring values.

Among the offspring of this union have been more vigorous and self-perpetuating features of growth and survival over the recent generations than have followed any other event in the social progress of our times.

Hardly had the guns and bugles of our Civil War ceased their clamor, and military uniforms been doffed for work-a-day clothes before there cropped up in the large cities of this country a harvest of new ideas and hopes, and a philosophy of social reconstruction worthy of the triumph of the spirit of union across the continent. Men who had experienced the devastations of battle, hunger and pestilence brought home from the army also vivid memories of the beneficent protection carried into bivouacs, hospitals and prison camps by the agents of the United States Sanitary Commission. Our young veterans recognized discipline and authority as indispensable to an effective use of the slender resources of medical science of the day.

It must be recalled that the germ of our own particular sanitary reconstruction had begun to grow before the outbreak of the Civil War. It was in fact on February 3, 1859 that the Senate of the State of New York received the report of its select committee, appointed in April of the previous year to investigate the Health Department of the City of New York.

Three facts were established in this report. The City of New York had a higher ratio of mortality than other large cities in this country and in Europe. The main causes of the excessive mortality were over-

* Delivered March 5, 1941 at the exercises commemorating the 75th Anniversary of the New York City Board of Health, in the Auditorium of the Health Building, Manhattan.

crowded tenement houses; want of practical knowledge of the proper mode of constructing such houses; deficiency of light; imperfect ventilation; impurities in domestic economy; unwholesome food and beverages; want of cleanliness in streets, and at wharves and piers; and finally a general disregard of sanitary precautions, imperfect execution of existing ordinances and a total absence of regularly organized efficient sanitary police. The remedy to be relied upon to bring health to the City was "the establishment of a thoroughly organized medical police, at whose head should be an active and experienced medical man."

The war brought this official effort, intelligent, constructive and promising as it was, to an abrupt end and it was not until 1865 that the even more deplorable state of the population and their housing was again studied with the results we are here assembled to commemorate.

It took but one year of concentrated well directed voluntary study of the prevalence of sickness and death in every block of the city by the physicians of New York to convince the Citizen's Association and the State Legislature that the day of corruption, incompetence and indifference must give way to a pattern of health service consistent with the ambitions and necessities of the nation's metropolis.

In thoroughness and in practical effect the classical Sanitary Survey of New York of 1865 has not been excelled, nor has any agency of public betterment in the past 75 years created as great or as permanent an effect upon the way of life and upon the use of government for social benefit as did the Council on Hygiene and Public Health which organized the study, published the report and made its conclusions effective by supporting the enabling legislation.

The following paragraph from that report reveals the sensitiveness of this body of surveying physicians to the value of voluntary as well as official efforts for the health of the city.

"Earnestly as we would strive to secure the application of adequate laws for the improvement and protection of the public health, we would, with equal earnestness, and for the same ends, urge that individual and organized efforts be put forth, for all these agencies must eventually cooperate in giving to the population of this city that protection to life and health which an enlightened people claim to be due to all classes of society."

It was the legal astuteness and the social statesmanship of a master of sanitary law, Dorman B. Eaton, that made good use of the opportunity

out of which came a body of such broad and adequate powers for public health control that they have needed little if any enlargement and have suffered no limitations since that date.

This was no trial marriage but a devoted union for better or worse until death do us part. In this spirit the medical sciences joined hands with the elder partner, the city government, with due formality of contract, and the Metropolitan Board of Health was the family name.

No well-read New Yorker needs to be reminded of "The City that Was," a political epic, a medical romance, a news thriller of relatively recent years wherein are told those stirring tales of Dr. Stephen Smith's success in outwitting landlords and aldermen and driving out of the cellars and cesspits of a dangerously overcrowded population the cruder forms of sanitary abuse. Almost unbelievable are the reports of school rooms with one-fourth the space we now think necessary for each child. There was the well-supported evidence of the first sanitary chemist, Professor Chandler, that a quarter of the milk sold consisted of more or less polluted tap water and for this water in their milk the people paid about four million dollars a year.

Epidemics of Texas fever decimated the cattle yards, the gas nuisance blighted large areas of workmen's homes, the kerosene lamp was a common fire hazard challenging sanitarians as well as underwriters. Even churches were so overcrowded as to threaten the health of congregations. More than one quarter of the samples of milk tested revealed gross physical and chemical adulteration. The ever-recurring threat of poisonous cosmetics, hair tonics and dyes, skin enamels and powders was old and familiar then as now to the health officers of the city. Equine influenza periodically swept away its thousands of horses.

It was the medical officers of the Health Department whose report upon the working conditions of horse-car drivers revealed with dramatic thoroughness the miserable barbarity of their employment from fifteen to seventeen hours a day on their feet behind the clanging dashboards. It was these same inspectors who studied the home and factory conditions of the tobacco industry and came to the conclusion that the home cigar-makers were better paid, had better food and in general lived better lives than was true of factory workers in the same trade.

It was the relative infertility among tobacco workers in general which was at that time a cause of more anxiety than any adverse health conditions found among them.

Truly the city of that day was a rapacious Moloch devouring the most vigorous and ambitious youth from our own farms and from the shiploads of immigrants. Death rates often exceeded birth rates and it was a very real question whether city life could exist on these terms. It remained to be proved whether such large gatherings of human beings could survive the very conditions upon which the wealth and culture of their days depended.

The answer did not come at once, nor has the challenge of man's arrogance in a metropolitan existence been permanently met in our time.

Even today, at the zenith of our health accomplishment the margin between living and dying is but slender and unstable. With birth rates of thirty-six and death rates of thirty-five per thousand of the population in some of the years of the first decade of the new regime it was difficult to prove the value of protective measures.

Man's struggle for survival has ever depended upon the accumulating treasury of knowledge of human biology of which the medical profession has been the self-perpetuating trustee and practitioner. Only as the facts of causes and effects became obvious were the innumerable handicaps to man's existence reduced by conscious control. Most of the information upon which the triumphs of the latter decades have been based was obscure or wholly lacking when the sanitarians of 1866 attacked the Augean stables that were then our city slums. There was but one certain and specific protection against an ancient and persistent pestilence, vaccination for the smallpox; and quinine and mercury were the only drugs for which true curative properties could be claimed. With the wisdom of a simple faith in communal cleanliness, in a fairer form of municipal housekeeping, the sanitary inspectors and the authors of sanitary ordinances set themselves to create an environment upon which could be built the finer structure of wholesome family life.

From the very beginning of the work of the Metropolitan Board of Health there was provision for fact-finding and original inquiry as the basis for public policy, the chemists first and soon after the microscopists laying the sound foundations for that unique creation within city government, so creditable to New York, the public health laboratory, out of which has grown so glorious an accomplishment and tradition.

With a sure eye for relative values, for the needs of first and urgent importance, the Board of Health established a permanent concern for

three of the standard functions of government health service, the record and analysis of the human family, our vital statistics, control of man's material envelope, or sanitation; and, most urgent at that time, protection against pestilence. These occupied the master rooms in our new house of health.

It was not until after the first quarter-century of growth that the fourth major function, the diagnostic laboratory was added to the enlarged mansion in 1892, to be followed just before the half-century by a spacious wing for childhood and maternity and for the latest member of the family, health education.

Whether or not by *words* exactly suited to our modern conception, the original Metropolitan Board of Health did by their *acts* define public health as the application of the sciences of preventive medicine by government for social ends. These physicians, chemists, engineers and lawyers of 1866 saw clearly the boundary between individual and administrative medicine; and while holding closely to their coöperative dependence upon the family and hospital physician, developed the use of public authority and tax resources for general as distinct from personal benefits. Without meticulous distinction between the curative and preventive resources of medicine they took pains to make their efforts supplementary and accessory to, rather than substitutes for the work of their colleagues of the private office, the public dispensary and the hospital ward.

Within six weeks of the organization of the Metropolitan Board of Health it declared "evidence of great and imminent danger to the public health by reason of impending pestilence" and requested the Governor of the State to extend to it extraordinary powers. Thus a cholera epidemic was for the first time in the city's history met by an informed professional leadership clothed with adequate authority and supplied with sufficient funds.

From that time forward the broad powers granted to the Board of Health by the legislature were tested in a multitude of crises of sanitation, politics and finance. Almost without exception, and certainly without substantial damage to its usefulness, the sanitary code of ordinances enacted by the Board, its enforcement of them and its quasi-judicial hearings on appeal against its orders have been supported and strengthened by the courts.

This Board of Health of the Metropolitan Sanitary District of the

State of New York became an *imperium in imperio* in all matters related in any way to the health of the people of this city, limited only by the proper restraint that its ordinances, and actions based upon them, should be neither arbitrary nor tyrannical. The legal structure was so sound and its support by the courts so general that it has served as a model for many another city and state as the basis for public health statutes and local ordinances. The counties of New York, Kings, Westchester and Richmond, and the towns of Newtown, Flushing and Jamaica, in the county of Queens were included in its jurisdiction.

Lest we indulge in unseemly and parochial self-laudation, it is well to recall that our critical date of 1865 for the Sanitary Survey, which was, let us say, the year of courting and betrothal that brought medicine and government to the desire or necessity of a New York marriage, was but the third in historical sequence, the Sanitary Survey of Massachusetts by Lemuel Shattuck of 1855 and the Sanitary Survey of the Labouring Population of Great Britain by Edwin Chadwick in 1842 having set the stage for the first basic state and national public health laws in the modern manner, as our physician's study did for a city community.

Medicine had its poets then, and sanitation had not gone unsung as these verses of Dr. Holmes bore witness at the meeting of the National Sanitary Association in 1860. Anatomist, surgeon, obstetrician, sanitarian, Oliver Wendell Holmes rang out a prophetic challenge which still awaits its adequate response.

"What makes the Healing Art divine?
The bitter drug we buy and sell;
The brands that scorch, the blades that shine,
The scars we leave, the 'cures' we tell?

"Are these thy glories, holiest Art,—
The trophies that adorn thee best,—
Or but thy triumph's meanest part,—
Where mortal weakness stands confessed?

"God lent his creatures light and air.
And waters open to the skies;
Man locks him in a stifling lair,
And wonders why his brother dies!

"In vain our pitying tears are shed,
In vain we rear the sheltering pile
Where Art weeds out from bed to bed
The plagues we planted by the mile!

"Be that the glory of the past;
With these our sacred toils begin;
So flies in tatters from its mast
The yellow flag of sloth and sin.

"And lo! the starry folds reveal
The blazoned truth we hold so dear:
To guard is better than to heal,–
The shield is nobler than the spear."

When we think of those early pioneers in municipal health administration, the collective bridegroom of the wedding of 1866, and while we still cling to their determination to make practical realities out of the potential blessings of medical science, in spite of the recurrent interruptions of war and its increasing present threat, we can say as Dr. Osler did at his farewell dinner in this city:

"What the future has in store for me I cannot tell, you cannot tell. Nor do I much care as long as I can carry with me, as I shall, the memory of the past you have given me. Nothing can take that away."

Nothing can deprive us, as we move on into the last quarter of our city's first century of health, of the sense of obligation, of the memory of performance, of high resolves, of the salvaging of multitudes which our ancestors of medicine and government achieved way back yonder, those 75 years ago.

Let us keep faith with those giants who built the home we occupy in great safety and much comfort, and devote ourselves with equal determination to "the building of a better tabernacle for the soul of man to inhabit," for such we are told by Sir George Newman of the British Ministry of Health is the purpose of preventive medicine.

May we say now and pledge our successors to declare that

"We have loved no darkness
Sophisticated no truth
Nursed no delusion
Allowed no fear."

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

Aldrich, C. A. & Aldrich, (Mrs.) M. (McCague). *Feeding our old fashioned children.*
N. Y., Macmillan, 1941, 112 p.

American College of Physicians. *The American College of Physicians; its first quarter century.*
Phil., [Amer. College of Physicians], 1940, 275 p.

Atkinson, T. G. *Visual field charting.*
Chic., Professional Press, [1941], 128 p.

Blood Transfusion Association. *Report concerning the project for supplying blood plasma to England.*
N. Y., Blood Transfusion Assoc., 1941, 121 p.

Bödecker, C. F. *Fundamentals of dental histology and embryology.* 2. ed.
N. Y., School of Dental and Oral Surgery, Columbia Univ., [1940], 249 p.

Bradley, C. *Schizophrenia in childhood.*
N. Y., Macmillan, 1941, 152 p.

Bram, I. *How to prevent goiter.*
N. Y., Dutton, 1941, 182 p.

Browning, (Mrs.) E. *Modern drugs in general practice.*
London, Arnold, [1940], 236 p.

Butt, H. R. & Snell, A. M. *Vitamin K.*
Phil, Saunders, 1941, 172 p.

Cameron, T. W. M. *The parasites of man in temperate climates.*
Toronto, Univ. of Toronto Press, 1940, 182 p.

Cardiac classics; a collection of classic works on the heart and circulation, [comp.] by F. A. Willius and T. E. Keys.
St. Louis, Mosby, 1941, 858 p.

Carlson, E. R. *Born that way.*
N. Y., Day, [1941], 174 p.

Carroll, R. S. *What price alcohol? A practical discussion of the causes and treatment of alcoholism.*
N. Y., Macmillan, 1941, 362 p.

Cleckley, H. M. *The mask of sanity.*
St. Louis, Mosby, 1941, 298 p.

Collier, H. E. *Outlines of industrial medical practice.*
London, Arnold, [1940], 440 p.

Colmeiro Laforet, C. *El diagnóstico precoz del embarazo.*
[Santiago de Compostela, Libreria Gali], 1940, 242 p.

Columbia University. DeLamar Institute of Public Health. *Population, births, notifiable diseases, and deaths, assembled for New York City . . . 1866-1938.*
N. Y., DeLamar Institute of Public Health, 1941, [406] l.

Condé, Jahn, F. *Oidos, nariz y garganta.* 2. series.
Caracas, Edit. Elite, 1941, 248 p.

Cosío Villegas, I. *Los abscesos del pulmon.*
México, Compañia General Editora, 1940, 147 p.

Davis, M. M. *America organizes medicine.*
N. Y., Harper, 1941, 335 p.

Diehl, H. S. *Healthful living.*
N. Y., Whittlesey, [1941], 499 p.

von Eicken, C. O. & Schulz van Treeck, A. *Atlas der Hals-, Nasen-, Ohrenkrankheiten.*
Leipzig, Thieme, 1940, 199 p.

Ellis, C. & Wells, A. A. *The chemical action of ultraviolet rays.* Rev. ed.
N. Y., Reinhold, 1941, 961 p.

Freud, S. *Schriften aus dem Nachlass,* 1892-1938.
London, Imago Pub. Co., 1941, 159 p.

Gaddum, J. H. *Pharmacology.*
London, Milford, 1940, 407 p.

Galloway, J. M. *Handbook of laboratory technic.*
Phil., Davis, 1941, 258 p.

Gibbs, F. A. & Gibbs, E. L. *Atlas of electroencephalography.*
[Cambridge, Mass., Cummings, 1941], 221 p.

Gifford, S. R. *A textbook of ophthalmology.* 2. ed.

Phil., Saunders, 1941, 470 p.

Griffith, J. P. C. & Mitchell, A. G. *Textbook of pediatrics.* 3. ed.
Phil., Saunders, 1941, 991 p.

Gruhle, H. W. *Selbstmord.*
Leipzig, Thieme, 1940, 166 p.

Gstirner, F. *Chemisch-physikalische Vitaminbestimmungsmethoden.* 2. Aufl.
Stuttgart, Enke, 1940, 226 p.

Hamilton, B. E. & Thomson, K. J. *The heart in pregnancy and the childbearing age.*
Boston, Little, 1941, 402 p.

Hill, R. B. & Benarroch, E. I. *Anquilostomiasis y paludismo en Venezuela.*
Caracas, Edit. Elite, 1940, 204 p.

Hoffman, W. S. *Photelometric clinical chemistry.*
N. Y., Morrow, 1941, 254 p.

Holzer, W. *Physikalische Medizin in Diagnostik und Therapie.*
Wien, Maudrich, 1940, 674 p.

Hoskins, R. G. *Endocrinology.*
N. Y., Norton, [1941], 388 p.

Hutchison, (Sir) R. *Food and the principles of dietetics.* 9. ed.
London, Arnold, [1940], 648 p.

James, W. W. & Fickling, B. W. *Injuries of the jaws and face, with special reference to war casualties.*
London, Bale, [1940], 199 p.

Johlin, J. M. *Introduction to physical biochemistry.*
N. Y., Hoeber, [1941], 231 p.

Joslin, E. P. *A diabetic manual.* 7. ed.
Phil., Lea, 1941, 238 p.

Kohlrausch, W. & Leube, H. *Lehrbuch der Krankengymnastik bei inneren Erkrankungen.*
Jena, Fischer, 1940, 248 p.

Kolmer, J. A. & Boerner, F. *Approved laboratory technic.* 3. ed.
N. Y., Appleton-Century, [1941], 921 p.

Kraines, S. H. *The therapy of the neuroses and psychoses.*
Phil., Lea, 1941, 512 p.

Krusen, F. H. *Physical medicine.*
Phil., Saunders, 1941, 846 p.

Laun, H. R. *Vademekum des Truppenarztes: erste Hilfe.* 3. Aufl.
München, Lehmann, 1940, 283 p.

Lennox, W. G. *Science and seizures; new light on epilepsy and migraine.*
N. Y., Harper, [1941], 258 p.

Lewis, N. D. C. *A short history of psychiatric achievement.*
N. Y., Norton, [1941], 275 p.

Loewenberg, S. A. *Clinical endocrinology.* 2. ed.
Phil., Davis, 1941, 883 p.

Loewenberg, S. A. *Medical diagnosis and symptomatology.* 5. ed.
Phil., Davis, 1941, 1139 p.

Luyet, B. J. & Gehenio, P. M. *Life and death at low temperatures.*
Normandy, Mo., Biodynamica, 1940, 341 p.

McCoy, J. D. *Applied orthodontics.* 5. ed.
Phil., Lea, 1941, 333 p.

Maguire, F. A. *The anatomy of the female pelvis.* 3. ed.
Sydney, Angus, [1940], 162 p.

Maslow, A. H. & Mittelmann, B. *Principles of abnormal psychology: the dynamics of psychic illness.*
N. Y., Harper, [1941], 638 p.

Military medical manual. 4. ed.
Harrisburg, Military Service Pub. Co., [1940], 877 p.

Modern diagnosis, edited by Sir H. Rolleston and A. Moncrieff.
London, Eyre, 1940, 286 p.

Morris, H. M. *Medical electricity.* 2. ed.
London, Churchill, 1941, 394 p.

Newman, B. M. *Must we grow old?*
N. Y., Putnam, [1941], 269 p.

Niemoeller, A. F. *Handbook of hearing aids.*
N. Y., Harvest House, 1940, 155 p.

Perla, D. & Marmorston, J. *Natural resistance and clinical medicine.*
Boston, Little, 1941, 1344 p.

Pintner, R.; Eisenson, J. & Stanton, M. *The psychology of the physically handicapped.*
N. Y., Crofts, 1941, 391 p.

Port, K. W. *Die sog[enannte] schwedische Massage; ihre Anwendung und ihre Erfolge.* 2. Aufl.
Stuttgart, Enke, 1941, 171 p.

Prinz, H. *Dental formulary.* 6. ed.
Phil., Lea, 1941, 352 p.

Reichenbach, E. *Leitfaden der Kieferbruchbehandlung.* 3. Aufl.
Leipzig, Barth, 1940, 174 p.

Rodenwaldt, E. R. K. *Tropenhygiene.* 2.

Aufl.
Stuttgart, Enke, 1941, 152 p.

Rohr, K. *Das menschliche Knochenmark.*
Leipzig, Thieme, 1940, 286 p.

Rosser, C. M. *Doctors and doctors, wise and otherwise.* [Autobiography].
Dallas, Mathis, [1941], 388 p.

Sigerist, H. E. *Medicine and human welfare.*
New Haven, Yale Univ. Press, 1941, 148 p.

Smith, E. A. *Building a dental practice.*
[N. Y.], author, [1941], 51 p.

Souttar, H. S. *The art of surgery.* 4. ed.
London, Heinemann, 1940, 2 v.

Special surgery in wartime, by D. W. C. Northfield [et al.].
London, Eyre, [1940], 74 p.

Storz, L. A. *Some early dental history of Worcester.*
Worcester, Mass., [Heffernan Press], 1941, 34 p.

Sturtevant, M. *Lectures on gastroenterology.* 3. ed.
Ann Arbor, Edwards, 1940, 113 p.

Sweany, H. C. *Age morphology of primary tubercles.*
Springfield, Ill., Thomas, 1941, 265 p.

Taylor, F. S. *The conquest of bacteria.* 2. ed.
London, Secker, 1940, 144 p.

Temperature, its measurement and control in science; papers presented at a symposium held . . . 1939 under the auspices of the American Institute of Physics.
N. Y., Reinhold, 1941, 1362 p.

Thoma, K. H. *Oral pathology.*
St. Louis, Mosby, 1941, 1306 p.

Timperly, W. A. *Haemophilia and egg-white derivatives.*
[Leeds, Jowett], 1940, 63 p.

Unger, H. *Unvergängliches Erbe; das Lebenswerk Emil von Behrings.*
Oldenburg, Stalling, [1941], 193 p.

United States. Public Health Service. *Manual of procedure for the mechanical system of reporting morbidity, treatment-progress and control of the venereal diseases.*
Wash., U. S. Public Health Service, 1940, 1 v.

United States. War Department. Medical Field Service School, Carlisle Barracks, Pa. Department of extension Courses. *Medical service of the division.*
[Carlisle Barracks, Med. Field Service School, 1940], 278 p.

United States. War Department. Medical Field Service School, Carlisle Barracks, Pa. Department of Military Sanitation. *Essentials of field sanitation.* Rev. ed.
[Carlisle Barracks, Med. Field Service School], 1940, 180 p.

Vaughan, W. T. *Strange malady, the story of allergy.*
N. Y., Doubleday, 1941, 268 p.

Vernon, H. M. *The health and efficiency of munition workers.*
London, Milford, 1940, 138 p.

Vigliani, E. C. *Studio sull' asbestosi nelle manifatture di amianto.*
[Ciriè, Capella], 1940, 74 p.

Waite, F. C. *History of the School of Dentistry of Western Reserve University.*
Cleveland, [Western Reserve Univ.], 1940, 223 p.

Weinberger, B. W. *Pierre Fauchard, surgeon-dentist.*
Minneapolis, Pierre Fauchard Academy, 1941, 102 p.

Weisman, A. I. *Spermatozoa and sterility.*
N. Y., Hoeber, [1941], 314 p.

Werner, B. C. F. *Das Labyrinth.*
Leipzig, Thieme, 1940, 400 p.

Weyl, C.; Warren, S. R. & O'Neill, D. B. *Radiologic physics.*
Springfield, Ill., Thomas, 1941, 459 p.

Williams, J. F. *Healthful living.* 3. ed.
N. Y., Macmillan, [1941], 600 p.

Yater, W. M. *The fundamentals of internal medicine.* 1. ed. [2.] rev.
N. Y., Appleton-Century, [1941], 1021 p.

Zischinsky, H. *Die akuten Infektionskrankheiten in Kindesalter.*
Stuttgart, Marquardt, 1940, 266 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 6—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Action on proposed amendment to Constitution. ¶ Scientific Program—Newer Surgery of the Heart and Large Vessels—a] Medical aspects, H. M. Marvin, Associate Clinical Professor of Medicine, Yale University School of Medicine; b] Surgical aspects, William DeWitt Andrus, Associate Professor of Surgery, Cornell University Medical College. ¶ Report on Election of Fellows.

FEBRUARY 20—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The fifth Harvey lecture, "The Significance of the Sulfur-Containing Amino Acids in Metabolism," Howard B. Lewis, Professor of Biological Chemistry, University of Michigan Medical School.

MARCH 6—*The New York Academy of Medicine.* Executive session—a] Reading of the minutes. ¶ Scientific Program—Current Concepts Regarding Benign Lesions of the Small Intestine—a] Roentgenological aspects, Ross Golden, Professor of Radiology, College of Physicians and Surgeons, Columbia University; b] Surgical aspects, Claude F. Dixon, Associate Professor of Surgery, Mayo Foundation, University of Minnesota; c] Medical aspects, Burrill B. Crohn, Associate in Medicine, The Mount Sinai Hospital. ¶ Report on Election of Fellows and Honorary Fellow.

MARCH 20—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The sixth Harvey lecture, "Some Cardiac Effects of the Inhalant Anesthetics and the Sympathomimetic Amines," Walter J. Meek, Professor of Physiology, University of Wisconsin.

APRIL 3—*The New York Academy of Medicine.* Executive Session—a] Reading of the minutes; b] Presentation of Certificates of Fellowship. ¶ The Sixteenth Hermann Michael Biggs Memorial Lecture, Clarence A. Mills, Professor of Experimental Medicine, University of Cincinnati College of Medicine on "The Relation of Climate and Geography to Health." ¶ Report on Election of Fellows.

APRIL 10—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The seventh Harvey lecture, "Hormones and the Process of Aging," Leo Loeb, Emeritus Professor of Pathology, Washington University School of Medicine.

SECTION MEETINGS

FEBRUARY 4—*Section of Dermatology and Syphilology.* Presentation of cases of syphilis of the skin and mucous membrane, in conjunction with the Health Department program for educating the profession in the diagnosis and treatment of syphilis. ¶ Discussion of cases. ¶ Executive session.

FEBRUARY 7—*Section of Surgery.* Reading of the Minutes. ¶ Presentation of cases—a] Carcinoma of ampulla of Vater, two years postoperative, John A. Timm (by invitation); Discussion, Pierre Renaud (by invitation); b] Stricture of the common bile duct with calculi. Symptoms simulating coronary disease. Operation—one year follow-up, Kenneth M. Lewis; Discussion, Morris K. Smith; c] (1) Acute cholecystitis, cholelithiasis in a girl, age 15; (2) Calcium carbonate gall-bladder, Edward D. Truesdell. ¶ Papers of the evening—a] Obstructive jaundice due to carcinoma of the pancreas: The choice of operative procedure, Myron A. Sallick, John H. Garlock; Discussion, Richard Lewisohn; b] The role of the liver in surgery, John H. Mulholland; Discussion, Murray MacG.

Gardner (by invitation). ¶ General discussion.

FEBRUARY 11—*Section of Neurology and Psychiatry.* Reading of the minutes. ¶ Presentation of case—Parkinson syndrome associated with hemiatrophy of central origin, Orman C. Perkins, Max Gold (by invitation); Discussion, Charles A. McKendree. ¶ Papers of the evening—a] A consideration of the surgical treatment of craniopharyngiomas, Jefferson Browder; Discussion, Ira Cohen; b] Occlusion of the sagittal sinus, Harold R. Merwarth; Discussion, Byron Stookey, J. E. J. King; c] Therapy in Parkinsonism; A critical evaluation, A. M. Rabiner, Morton Hand (by invitation). ¶ General discussion. ¶ Executive session.

FEBRUARY 13—*Section of Pediatrics.* Reading of the minutes. ¶ Papers of the evening—a] Weak feet, weak ligaments, and poor posture, George L. Inge; Discussion, Katharine G. Dodge; b] Joint tuberculosis: diagnosis and treatment, Alan deF. Smith; Discussion, Mather Cleveland; c] Congenital dislocation of the hip, Beckett Howorth; Discussion, T. Campbell Thompson; d] Scoliosis, William H. von Lackum (by invitation); Discussion, John R. Cobb.

FEBRUARY 17—Section of Ophthalmology. ¶ Exhibits 7:00 to 8:30 o'clock—a] Demonstration of fluorescence of lens material and of certain lesions, with long-wave ultraviolet, Eliott B. Hague, Buffalo (by invitation); b] Histology studies of grafted eyes and regenerating lenses, L. S. Stone, New Haven (by invitation); c] Colored photomicrographs of the ocular blood vessels, Robert K. Lambert; d] Slit lamp cases, Milton L. Berliner, Gordon M. Bruce, Girolamo Bonaccolto, Sidney Fox (by invitation). ¶ Executive Session; ¶ Presentation of cases—a] Three cases of Kaiser-Fleischer Ring in hepatolenticular degeneration, Samuel Gartner (by invitation); b] Hemangioma of orbit, Donald W. Bogart (by invitation); c] Squamous cell carcinoma of cornea, Samuel Evans (by invitation). ¶ Papers of the evening—a] The anatomy and functional significance of the primary endings of the optic nerve in man and animals (lantern slides), Otto Marburg (by invitation); b] Procedures in intracapsular cataract extraction, Daniel B. Kirby; c] Return of vision in the vertebrate eye following repeated transplantations (colored motion picture), L. S. Stone, New Haven (by invitation); d] special features of the ocular blood vessels, Robert K. Lambert.

FEBRUARY 18—*Section of Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Observations on the pathologic physiology of the human pancreas, Louis Bauman; Discussion, Allen O. Whipple; b] Paravertebral sympathetic block with alcohol for the relief of cardiac pain, Robert L. Levy, Richmond L. Moore (by invitation); Discussion, Harold J. Stewart, Bronson S. Ray. ¶ General discussion. ¶ Executive session.

FEBRUARY 19—*Section of Genito-Urinary Surgery.* Reading of the minutes. ¶ Papers of the evening—a] Urinary extravasation, Edward O. Finestone (by invitation); b] Hemangioma of the urinary bladder, with coincident papillary carcinoma (case report), Joseph A. Hyams; c] Lymphosarcoma of the prostate and epididymis (case report), Joseph Tenenbaum; d] Actinomycosis of the kidney (case report), Frederick T. Bond (by invitation); e] Triplication of the renal pelvis and ureter on the right side (case report), Stanley R. Woodruff, Jersey City. ¶ General discussion. ¶ Executive session.

FEBRUARY 19—*Section of Otolaryngology.* Reading of the minutes. ¶ Papers of the evening—a] Non-surgical treatments for deafness: 1. Psychotherapy, prostigmin, radiotherapy, Edmund P. Fowler, Jr.; 2. Drugs, vitamins, endocrines, prostheses, William A. Greenfield (by invitation); b] The consequences of shortened intermaxillary dis-

tance, H. R. Junemann, D.D.S. (by invitation); c] What is being done for deafness of school children, Westley M. Hunt; d] Incidence of surgical procedures using acute mastoiditis as an indicator—a study over a period of eleven years with detailed statistics for New York and other geographic sections of the United States, Harold W. Corya (by invitation); Discussion, Marvin F. Jones, William H. Best (by invitation). ¶ General discussion.

FEBRUARY 21—*Section of Orthopedic Surgery.* Reading of the minutes. ¶ Papers of the evening—a] The intermuscular lateral approach for removal of cervical rib, Samuel Kleinberg; b] Anatomical evaluation of symptoms due to cervical rib, Russel H. Patterson; c] The scalenus anticus syndrome with and without cervical rib, report of 25 cases, J. M. Donald (by invitation), Birmingham, Alabama. ¶ Discussion, Kristian G. Hansson (by invitation), Clement B. Masson. ¶ General discussion.

FEBRUARY 25—*Section of Obstetrics and Gynecology.* Executive session—reading of the minutes. ¶ Papers of the evening (Program by Bellevue Hospital, Department of Obstetrics and Gynecology), Prevention and treatment of puerperal infection—a] Method of prevention of postpartum infection, George Bowen (by invitation); b] Treatment of group "A" hemolyticus streptococcus infection in the puerperal state, Gerhard Ahnquist (by invitation); c] Severe anaerobic streptococcus septicemia in the puerperium with recovery (a case report), Hiram Salter (by invitation); d] Bacteriological characteristics of anaerobic streptococcus recovered from postpartum patients, Melvin L. Stone (by invitation). ¶ Discussion, Thomas Francis, Jr.

MARCH 4—*Section of Dermatology and Syphilology.* Executive session — a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Presentation of cases—a] City Hospital; b] Polyclinic Hospital; c] Miscellaneous cases. ¶ Discussion of cases.

Section of Pediatrics. There was no meeting of the Section in March because of (1) the meeting of the American Academy of Pediatrics (Region 1) at New Haven, Conn., on March 27, 28 and 29, and (2) the joint meeting with the Section of Obstetrics and Gynecology and the New York Pathological Society in April, in addition to the regular meeting.

Section of Surgery. The March meeting of the Section was not held on the regular date. Instead, the Section of Surgery held a combined meeting with the Section of Medicine on March 18 (q.v.).

MARCH 11—*Combined Meeting: Section of Neurology and Psychiatry and the New York Neurological Society.* Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Papers of the evening—a] The effect of liver therapy on the pathways of the spinal cord in subacute combined degeneration, Charles Davison; Discussion, Lewis D. Stevenson; b] The psychopathology of psychopathic personality, George S. Sprague; Discussion, Karl M. Bowman, A. A. Brill; c] Ambulatory schizophrenias, Gregory Zilboorg; Discussion, A. A. Brill. ¶ General discussion.

MARCH 12—*Section of Historical and Cultural Medicine.* Executive session—a] Reading of the minutes; b] Report of Nominating Committee. ¶ Paper of the evening—Diseases in the Five Books of Moses, in the light of Egyptian medical papyri, Abraham S. E. Yahuda. ¶ General discussion.

MARCH 17—*Section of Ophthalmology.* Exhibits—a] Results of treatment of tumors in the region of the eye by irradiation, William Law Watson; b] Gross specimens of ocular neoplasms, Pathology Department, New York Eye and Ear Infirmary, Edgar Burchell (by in-

vitation); c] Tumors of the eye, lids, and orbit, Pathology Department, Institute of Ophthalmology, Charles A. Perera, John S. McGavic (by invitation). Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. Memorial to Dr. A. Edward Davis by Clyde E. McDannald. ¶ Papers of the evening: *Tumors of the Eye and Adnexa*—a] The eyeball, Theodore L. Terry, Boston, Mass. (by invitation); b] The orbit, C. S. O'Brien, Iowa City, Iowa (by invitation); c] the lids and conjunctiva, Bernard Samuels; d] Discussion, James Ewing.

MARCH 18—*Combined Meeting: Sections of Medicine and Surgery.* Executive session—a]Reading of the minutes; b] Appointment of Nominating Committee for each Section. ¶ Papers of the evening—a] The functional evaluation of renal disease in hypertension: 1. Bilateral studies, William Goldring; 2. Unilateral studies, Herbert Chasis (by invitation); b] Arterial hypertension—definition of the problem, Henry A. Schroeder (by invitation); c] Surgical treatment of hypertension, (presentation of cases), Carnes Weeks; d] Nephrectomy for arterial hypertension, George W. Fish; e] Surgical treatment of hypertension, Frank Glenn; f] Splenonephropexy in experimental and human hypertension, David M. Weeks; Discussion, Homer F. Smith. ¶ General discussion.

MARCH 19—*Section of Genito-Urinary Surgery.* Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Papers of the evening: *Symposium on Postoperative Complications*—a] The cardiac and pulmonary complications of urological surgery, Edwin P. Maynard, Jr., Brooklyn; Discussion opened by William H. Lohman, Brooklyn; b] Water balance and shock, Walter G. Maddock, University Hospital, Ann Arbor, Michigan (by invitation); Discussion opened by George F. Cahill. ¶ General discussion.

Section of Otolaryngology. Instead of the regular meeting of the Section of Otolaryngology at the Academy, the Section held a combined meeting with the Section on Otolaryngology of the College of Physicians of Philadelphia at their building in Philadelphia, March 19. ¶ Papers of the evening—a] Some interrelationships of otolaryngology and hematology, Thomas Fitz-Hugh, Jr., Discussion, Andrew A. Eggston; b] Some external nasal deformities and methods used in their repair, Warren B. Davis, Discussion, Arthur Palmer; c] Pharmacology and toxicology of the sulfonamide compounds, Harrison F. Flippin (by invitation), Discussion Wesley C. Bowers. Executive session—Appointment of Nominating Committee.

MARCH 21—*Section of Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Papers of the evening—a] Acromioclavicular separation. New method of repair. Illustrated by moving pictures, Boardman M. Bosworth; b] Deformities of the femur resulting from arrestment of growth, Edward L. Compere, Chicago, Illinois (by invitation); c] Aseptic necrosis and bone drilling, Ernst W. Bergmann (by invitation), Discussion, Alan De Forest Smith, Donald E. McKenna. ¶ General discussion

MARCH 25—*Section of Obstetrics and Gynecology.* Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶ Papers of the evening—a] Fracture of the femoral neck following roentgen therapy for gynecological malignancy, Hyman Strauss (by invitation), Joseph L. McGoldrick (by invitation), Discussion, Maurice Lenz, William P. Healy; b] The theca-interna cone and the ascensus of the Graafian follicle, Erwin O. Strassmann, Houston, Texas (by invitation), Discussion, Alfred Plaut, Herbert Traut, Grete Stohr (by invitation).

APRIL 1—*Section of Dermatology and Syph-*

ilology. Executive session—Nomination of Section Officers and one member of Advisory Committee. ¶Presentation of cases—The Skin and Cancer Unit of Post-Graduate Hospital. ¶Discussion of cases.

April 4—*Section of Surgery.* Executive session—a] Reading of the Minutes; b] Nomination of Section Officers and one Member of Advisory Committee. ¶Presentation of cases—a] Aneurysm of splenic artery—removal—recovery, Irwin E. Siris, Discussion, Leo Loewe; b] Leiomyosarcoma of the stomach, Edwin B. Eckerson, Discussion, Thomas H. Russell; c] Pyloric obstruction caused by heterotopia of Brunner's glands, James H. Kidder (by invitation), Discussion, Harold B. Keyes; d] Non-specific ileitis —resection—apparent cure, Gaston A. Carlucci, Discussion, Lester Breidenbach. ¶Papers of the evening—a] Surgical problems in the treatment of gastrojejunal ulcers, Ralph Colp, Discussion, John J. Westermann, Jr.; b]Benign tumors of the stomach, Laurence Miscall, Discussion, Guilford S. Dudley. ¶General discussion.

April 8—*Section of Neurology and Psychiatry.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶Presentation of cases—Cerebellar agenesis, Ira Cohen. Discussion, H. A. Riley. ¶Papers of the evening—a] Peculiarities of the blood plasma in cases of multiple sclerosis, Tracy J. Putnam, William S. Orr (by invitation), Mildred G. Gray, Ph D. (by invitation); b] Fiber dissociation in peripheral neuropathy, Herman Wortis, Martin Stein (by invitation), Norman Jolliffe; Discussion, E. D. Friedman, Louis Hausman. ¶General discussion.

April 10—*Section of Pediatrics.* Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶Papers of the evening—a] Behavior disorders associated with intracranial tumors in childhood (case reports), William S. Langford (by invitation), Discussion, Lauretta Bender; b] Late results of the treatment of infantile hydrocephalus by endoscopic coagulation of the choroid plexuses, Tracy J. Putnam, Discussion, John E. Scarff; c] Acute encephalitis of unknown origin with cerebellar symptoms in children, Walter O. Klingman, Richard G. Hodges (by invitation); Discussion, Peter G. Denker.

This Section also held a joint meeting April 22, with the Section on Obstetrics and Gynecology, the New York Pathological Society, and the New York City Committee on Prematurity. See program under Section of Obstetrics and Gynecology.

April 15—*Section of Medicine.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶Papers of the evening—a] Modern clinical evaluation of liver diseases, Franklin M. Hanger, Discussion, Alexander B. Gutman; b] Diabetes and tuberculosis, Herman O. Mosenthal, Morton F. Mark (by invitation), Discussion, Edward Tolstoi. ¶General discussion.

April 16—*Section of Genito-Urinary Surgery.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶Papers of the evening—a] Division of renal isthmus in horseshoe kidney (case report), Robert Gutierrez; b] The management of ureteral calculi, with report of five cases of vaginal-uretero lithotomy, Edward W. Campbell, Philadelphia (by invitation). ¶General discussion.

April 16—*Section of Otolaryngology.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶Presentation of cases—Paraffinoma of the nose, George D. Wolf. ¶Papers of the evening—a] The "Illusion of Loudness" of tinnitus, its etiology, significance and treatment, Ed-

mund Prince Fowler, Discussion, R. Lorente de Nó (by invitation); b] Acute infections of the jaws, Francis S. McCaffrey, D.D.S.; c] Fractures of the maxillary bones, Douglas B. Parker (by invitation); d] Maxillary sinusitis of oral origin, closure of oro-antral openings, Henry S. Dunning. ¶ General discussion.

APRIL 18—*Section of Orthopedic Surgery.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. ¶ Papers of the evening—a] Calcareous tendinitis of the hand, William Cooper (by invitation); b] Low-grade multiple tuberculous lesions of bones and joints in children, Walker Ely Swift; c] Occurrence of pseudarthroses in the Hibb's spinal fusion operation, Walter A. L. Thompson (by invitation); d] Analysis of causes of failure in arthrodeses of tuberculous joints, Ernest E. Myers (by invitation), Discussion, Joseph B. L'Episcopo, David M. Bosworth. ¶ General discussion.

APRIL 21—*Section of Ophthalmology.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee. In memoriam—Herbert W. Wootton—David H. Webster. ¶ Presentation of cases—a] Marginal dystrophy of cornea, William W. Fitzgerald (by invitation); b] A case of lateral proboscis with a demicyclops, Rudolf Aebli, Louise H. Meeker. ¶ Papers of the evening—a] Photoreceptors of vertebrates, S. R. Detwiler (by invitation); b] The ocular signs of intracranial saccular aneurysms, Frank B. Walsh, Baltimore (by invitation); c] The surgical treatment of orbital plexiform neurofibromatosis, Edmund B. Spaeth, Philadelphia (by invitation).

APRIL 22—*Combined Meetings—Section of Obstetrics and Gynecology, Section of Pediatrics, New York Pathological Society and the New York City Committee on Prematurity.* Executive session—a] Reading of the minutes; b] Nomination of Section Officers and one member of Advisory Committee, for each Section. ¶ Papers of the evening—a] The pathology of the premature infant, Sidney Farber, Harvard Medical School (by invitation); b] The Chicago plan for reduction of infant mortality, Edith L. Potter, University of Chicago, School of Medicine (by invitation). ¶ Discussion, Rustin McIntosh, Beryl H. Paige, William E. Studdiford.

AFFILIATED SOCIETIES

FEBRUARY 17—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* ¶ Papers of the *evening*—a] Normal encephalogram, Cornelius G. Dyke; b] Abnormal encephalogram and surgical findings, Leo M. Davidoff (by invitation). ¶ Discussion, S. B. Wortis (by invitation), Bronson S. Ray (by invitation), Thomas Hoen (by invitation), Louis Stevenson (by invitation). ¶ Executive session.

FEBRUARY 27—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* ¶ Paper of the evening—Studies on the relation of the kidney to cardiovascular disease, M. C. Winternitz (by invitation), Yale University School of Medicine; Discussion, Homer Smith (by invitation), Irving Graef. ¶ Executive session.

MARCH 17—*New York Roentgen Society (in affiliation with The New York Academy of Medicine).* ¶ Papers of the evening; a] Tuberculosis of the breast treated by roentgen therapy, Samuel Richman; b] Radium dosimetry according to the method of Paterson and Parker, Sidney M. Silverstone (by invitation); c] Further experiences with contact (short distance) therapy, William Harris; d] Treatment of cancer of the larynx: (1) with fixed cord, (2) with subglottic disease, (3) total laryngectomy after radiation therapy, Rudolph Kramer. ¶ Discussion, Edith H.

Quimby, Carl Braestrup, John D. Kernan, Maurice Lenz. Executive session.

MARCH 27—*New York Pathological Society (in affiliation with The New York Academy of Medicine).* ¶ Papers of the evening—a] Histological changes produced in squamous cell epitheliomas of the mouth and oropharynx by fractionated external irradiation, John W. Hall (by invitation), Milton Friedman (by invitation), New York University Medical College; b] Tumors of the eye, Algernon B. Reese (by invitation), Institute of Ophthalmology of the Presbyterian Hospital. Executive session.

APRIL 21—*New York Roentgen Society (in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening; a] A survey of radiation protection in forty-five hospitals, L. Scheele (by invitation), D. B. Cowie (by invitation); b] X-ray protection in diagnostic radiology, C. B. Braestrup (by invitation). ¶ Discussion—a] Electrical protection, H. B. Williams (by invitation); b] Tube construction, R. R. Machlett (by invitation); c] Protection with intermediate and high voltage, I. H. Blatz (by invitation); d] Protection with supervoltage, T. R. Folsom (by invitation). Executive session.

APRIL 22—*The New York Pathological Society (in affiliation with The New York Academy of Medicine), held a joint meeting with the Section of Obstetrics and Gynecology, the Section of Pediatrics and the New York City Committee on Prematurity. See program under Section of Obstetrics and Gynecology.*

DEATHS OF FELLOWS

GILMOUR, ANDREW JAMES: 121 East 60 Street, New York City; born in Fulton, New York, March 1, 1871; died in New York City, March 9, 1941; received the degree of Ph.B. from Yale University in 1895; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1899; elected a Fellow of the Academy April 1, 1909.

Dr. Gilmour was consulting dermatologist to the Englewood Hospital and dermatologist to the Manhattan State Hospital. He was a diplomate of the American Board of Dermatology, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

WOOTTON, HERBERT WRIGHT: Old Lyme, Connecticut; born in New York City, December 25, 1867; died in Old Lyme, Connecticut, February 28, 1941; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1888; elected a Fellow of the Academy May 7, 1896 and served the Section of Ophthalmology as its Secretary from January 1906 to January 1909, and as its Chairman from January 1910 to January 1912.

Dr. Wootton was at one time professor of ophthalmolgy and director of surgery of the Manhattan Eye, Ear and Throat Hospital, and consulting ophthalmologist to the Willard Parker, Riverside and Gouverneur Hospitals, the U. S. Marine Hospital #70 and the Kingston Avenue Hospital in Brooklyn. He was a member of the American Ophthalmological Society, the New York Ophthalmological Society, the County and State Medical Societies of New York, and a Fellow of the American Medical Association.